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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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[X] Additional inventors are being named on the separately numbered sheet(s) attached hereto

TITLE OF THE INVENTION (280 characters max)

CRYSTALLINE SALTS OF CELECOXIB

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Attorney's Docket No: 3151.1004-003

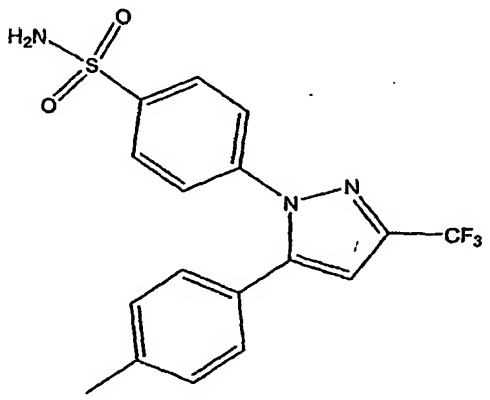
CRYSTALLINE SALTS OF CELECOXIB

INCORPORATION BY REFERENCE

The contents of U.S. Application No. 60/390,881, filed June 21, 2002, U.S. Application No. 60/426,275, filed November 14, 2002, and U.S. Application No. 60/427,086, filed November 15, 2002 are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) is a substituted pyrazolylbenzenesulfonamide represented by the structure:



Celecoxib belongs to the general class of non-steroidal anti-inflammatory drugs (NSAIDs). Unlike traditional NSAIDs, celecoxib is a selective inhibitor of cyclooxygenase II (COX-2) that causes fewer side effects when administered to a subject. The synthesis

and use of celecoxib are further described in U.S. Pat. Nos. 5,466,823, 5,510,496, 5,563,165, 5,753,688, 5,760,068, 5,972,986, and 6,156,781, the contents of which are incorporated by reference in their entirety. Orally deliverable liquid formulations of celecoxib are discussed in U.S. Patent Application Publication No. 2002/0107250 in the name of Hariharan, et al., the contents of which are incorporated herein by reference in their entirety.

In its commercially available form as Celebrex™, celecoxib is a neutral molecule that is essentially insoluble in water. Celecoxib typically exists as needle-like crystals, which tend to aggregate into a mass. Aggregation occurs even when celecoxib is mixed with other substances, such that a non-uniform mixture is obtained. These properties present significant problems in preparing pharmaceutical formulations of celecoxib, particularly oral formulations.

It would be advantageous to have new forms of celecoxib that have better properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of celecoxib that exhibit significantly increased water solubilities. It is also desirable to increase the dissolution rate of celecoxib-containing pharmaceutical compositions in water, increase the bioavailability of orally-administered celecoxib, and provide a more rapid onset to therapeutic effect. It is also desirable to have a salt of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide which when administered to a subject reaches a peak plasma level faster and/or has a longer lasting plasma concentration and higher overall exposure at high doses when compared to equivalent amounts of the celecoxib obtained from Celebrex™.

SUMMARY OF THE INVENTION

It has now been found that a stable, crystalline sodium salt of celecoxib can be synthesized, as shown in Example 1. The sodium salt of celecoxib prepared by Example 1 has been additionally found to convert to an amorphous free form of celecoxib upon neutralization of the salt, which subsequently converts to a neutral metastable crystalline form. These amorphous and metastable crystalline forms of neutral celecoxib are more

readily available forms of the drug than is presently-marketed neutral celecoxib. Neutral celecoxib is presently-marketed as Celebrex™, and is designated as "neutral" to distinguish it from the ionized salt form of celecoxib. In addition, it has been found that acidification or neutralization of a solution of the celecoxib salt *in situ* yields amorphous celecoxib, which subsequently converts to a metastable crystalline form of neutral celecoxib before finally converting into stable, presently-marketed neutral celecoxib.

It has additionally been found in rat studies that an orally administered 1:4 by weight blend of a sodium salt of celecoxib and polyvinylpyrrolidone reaches a peak plasma level of celecoxib faster than orally administered Celebrex™ (Example 4). Surprisingly, the same pharmacokinetic study found that, at 30 minutes following oral administration, the plasma concentration of celecoxib from the sodium salt was approximately four times greater than the plasma concentration of celecoxib from Celebrex™. A study conducted in dogs (Example 7, Figs. 5 and 6) similarly showed that bioavailability and maximum serum concentration of celecoxib were significantly higher for a formulation containing celecoxib sodium, as compared to a formulation containing neutral celecoxib.

The present invention includes a composition comprising a metal salt of celecoxib, wherein the salt is substantially more soluble in water than neutral celecoxib. Preferably, the salt transforms or converts into amorphous neutral celecoxib after contacting acidic, neutral, or weakly basic (e.g., pH less than about 11, pH less than about 10, pH less than about 9) solution. Often amorphous neutral celecoxib transforms or converts into neutral metastable crystalline celecoxib. Typically, metastable crystalline neutral celecoxib transforms or converts into stable crystalline neutral celecoxib (e.g., presently-marketed celecoxib), but an object of the present invention is to delay or prevent the formation of such stable crystalline neutral celecoxib. Salts of celecoxib can also include a polymorph, co-crystal, solvated co-crystal, hydrated co-crystal, desolvated co-crystal, dehydrated co-crystal, solvate, desolvate, hydrate, dehydrate, or anhydrous form of the salt.

Other salts of celecoxib included in the present invention include sodium salts, as characterized by powder x-ray diffraction spectra having peaks at 2-theta angles of 6.4°,

7.0°, 16.7°, and 20.9 ° (see Example 1); 4.1°, 5.0°, 6.5°, 10.0°, and 11.6°, (see Example 2); or 3.6°, 8.9°, 9.6°, 10.8°, 11.4°, and 20.0° (see Example 3).

In other embodiments, the present invention is a salt of celecoxib and a method of preparing a salt of celecoxib, where the salt is prepared by a process comprising the steps of:

1) contacting celecoxib with a solvent;

2) reacting celecoxib with greater than one equivalent of one or more bases, such that celecoxib dissolves; and

3) removing said solvent, thereby obtaining crystals of said salt of celecoxib.

In a preferred embodiment, the solvent is removed by evaporation. In another preferred embodiment, the solvent is removed by filtration (e.g., suction filtration).

The present invention also includes a method of treating a subject suffering from pain, inflammation or cancer or precancer (e.g., intestinal or colonic polyps), comprising administering to the subject a salt of celecoxib, wherein the salt is substantially more soluble in water than neutral celecoxib and wherein the salt reduces pain within 30 minutes. In a preferred embodiment, the salt is administered to the patient orally.

In another embodiment, the present invention is a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a salt of celecoxib, wherein the salt is substantially more soluble in water than presently marketed neutral celecoxib. Pharmaceutical compositions can optionally comprise one or more salts of celecoxib. In one preferred embodiment, the carrier or diluent is a polymer comprising one or more amide, ester, ketone, alcohol or ether functional groups. In another preferred embodiment, the carrier or diluent is a surfactant.

The present invention also includes a method of delivering a stable precursor of a quickly acting bioavailable form of celecoxib. Preferably, a quickly acting form of celecoxib exhibits a therapeutic effect within about 30 minutes. Similarly, the present invention includes a stable precursor of a quickly acting bioavailable form of celecoxib, where the stable precursor is a salt of celecoxib. In general, stable precursors can be a salt of celecoxib of the present invention.

In another embodiment, the invention includes a method of retarding the formation of neutral celecoxib crystals in a solution of a sodium salt of celecoxib, comprising the steps of:

a) contacting said salt with a polymer comprising one or more amide, ester, ether, alcohol or ketone functional groups; and

b) dissolving said salt in an aqueous solution.

Steps (a) and (b) can occur sequentially (e.g., step (a) then step (b) or step (b) then step (a)) or simultaneously. Preferably, the polymer contains one or more amide groups.

In yet another embodiment, the present invention is a pharmaceutical composition comprising a metal salt of celecoxib, where the metal salt of celecoxib is neutralized upon contact with water and forms an amorphous neutral celecoxib, an excipient which solubilizes said metal salt of celecoxib, and an excipient which inhibits said crystallization of the amorphous neutral celecoxib. In a specific embodiment, the pharmaceutical composition comprises a sodium salt of celecoxib, d-alpha-tocopherol polyethylene glycol-1000 succinate, and hydroxypropylcellulose. The invention also provides for a method of treating pain, inflammation, or cancer comprising the step of administering the above composition to a subject.

One advantage of the present invention is a method of preparing a salt of celecoxib. Additional advantages of the present invention include the ability to prepare a form of celecoxib from pharmaceutically-acceptable substances having reduced time to onset of therapeutic effectiveness and likely having increased bioavailability, which is also suitable for administration to subjects (e.g., human subjects). The present invention also provides a form of celecoxib that is stable enough to be stored for extended periods, but rapidly transforms into a more readily-absorbed, amorphous or metastable neutral form *in vivo* or when dissolved in neutral, acidic, or weakly basic solution.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a differential scanning calorimetry trace of the sodium salt of celecoxib prepared by Example 1 between 50°C and 110°C.

Fig. 2 shows a thermogravimetric analysis of the sodium salt of celecoxib prepared by Example 1, which was conducted from about 30°C to about 160°C.

Fig. 3 shows a powder x-ray diffraction plot of the sodium salt of celecoxib prepared by Example 1.

Figs. 4A and 4B show pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, as obtained following the protocol described in Example 4.

Fig. 5 shows the mean pharmacokinetic parameters (and standard deviations therefor) of celecoxib in the plasma of male dogs following a single oral or single intravenous dose of celecoxib or celecoxib sodium. The maximum serum concentration and bioavailability of orally-administered celecoxib sodium was about three- and two-fold greater, respectively, than a roughly equal dose of orally-administered celecoxib, and the maximum serum concentration of celecoxib sodium was reached 40% faster than for celecoxib.

Fig. 6 shows the mean concentrations of celecoxib in plasma following the administration of a single oral dose of celecoxib or celecoxib sodium or a single intravenous dose of celecoxib in male dogs.

Fig. 7 shows the effect of varying ratios of ethylene glycol to propylene glycol subunits in poloxamers on the concentration of celecoxib sodium in solution.

Fig. 8 shows the effect of different celluloses on the dissolution of various composition comprising equal weights of cellulose (hydroxypropylcellulose (HPC, 100,000 kDa), low-density hydroxypropylmethylcellulose (ld HPMC, viscocity was 80-120 cps), high-density hydroxypropylmethylcellulose (hd HPMC, viscosity was 15,000 cps), microcrystalline cellulose (Avicel PH200)), d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), and celecoxib sodium.

Fig. 9 shows the dissolution at 37°C for compositions comprising various weight ratios of d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose and celecoxib sodium.

Fig. 10 shows the dissolution profile of celecoxib sodium in simulated gastric fluid (SGF) from solid mixtures with excipients at room temperature. The legend indicates the excipient and the weight ratio of excipient to celecoxib sodium (if unmarked, 1:1). Excipients include polyvinylpyrrolidone (PVP), poloxamer 188 (P188), poloxamer 237 (P237), d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and Gelucire™ 50/13.

Fig. 11 shows the effect of Avicel microcrystalline cellulose and silica gel on the dissolution of mixtures of celecoxib sodium, d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and hydroxypropylcellulose (HPC) mixtures in simulated gastric fluid (SGF) at 37°C. The legend indicates the weight ratios of the components.

Fig. 12 shows the dissolution of celecoxib sodium (TPI336Na) in 5-times diluted simulated gastric fluid, with excipients including d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose (HPC), and poloxamer 237. the legend indicates the weight ratios of the components.

Figs. 13A and 13B shows the particle-induced x-ray diffraction (PXRD) and raman spectra, respectively, of the sodium salt of celecoxib prepared by the method of Example 6.

Fig. 14 shows a differential scanning calorimetry analysis of celecoxib lithium salt MO-116-49B.

Fig. 15 shows a thermogravimetric analysis of celecoxib lithium salt MO-116-49B.

Fig. 16 shows the RAMAN spectrum of celecoxib lithium salt MO-116-49B.

Fig. 17 shows the PXRD spectrum of celecoxib lithium salt MO-116-49B.

Fig. 18 shows a differential scanning calorimetry analysis of celecoxib potassium salt MO-116-49A.

Fig. 19 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-49A.

Fig. 20 shows the RAMAN spectrum of celecoxib potassium salt MO-116-49A.

Fig. 21 shows the PXRD spectrum of celecoxib potassium salt MO-116-49A.

Fig. 22 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-55D.

Fig. 23 shows the RAMAN spectrum of celecoxib potassium salt MO-116-55D.

Fig. 24 shows the PXRD spectrum of celecoxib potassium salt MO-116-55D.

Fig. 25 shows a thermogravimetric analysis of celecoxib calcium salt MO-116-62A.

Fig. 26 shows the RAMAN spectrum of celecoxib calcium salt MO-116-62A.

Fig. 27 shows the PXRD spectrum of celecoxib calcium salt MO-116-62A.

Fig. 28 shows the PXRD spectrum of commercially-available celecoxib.

Fig. 29 shows the RAMAN spectrum of commercially-available celecoxib.

Fig. 30 shows a differential scanning calorimetry analysis of a co-crystal of celecoxib and saccharin.

Fig. 31 shows a thermogravimetric analysis of a co-crystal of celecoxib and saccharin.

Fig. 32 shows the RAMAN spectrum of a co-crystal of celecoxib and saccharin.

Fig. 33 shows the PXRD spectrum of a co-crystal of celecoxib and saccharin.

Fig. 34 shows overlapping differential scanning calorimetry analyses of celecoxib, saccharin, and a co-crystal of the two.

Fig. 35 shows the RAMAN spectrum of a co-crystal of celecoxib and saccharin.

Fig. 36 shows the RAMAN spectrum of saccharin.

Fig. 37 shows the PXRD spectrum of saccharin.

Fig. 38 shows the PXRD spectrum of a co-crystal of celecoxib and saccharin.

Fig. 39 shows the PXRD spectrum of commercially-available celecoxib.

Fig. 40 shows a summary of the powder diffraction (PXRD) data depicted in Figs. 37-39.

Fig. 41 shows a thermogravimetric analysis of a propylene glycol solvate a of celecoxib sodium salt.

Fig. 42 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 43 shows a thermogravimetric analysis a propylene glycol solvate of a celecoxib potassium salt.

Fig. 44 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib potassium salt.

Fig. 45 shows a thermogravimetric analysis of a propylene glycol solvate of a celecoxib lithium salt.

Fig. 46 shows the area-under-the-curve (AUC) values for celecoxib in dogs from various dosage forms versus the oral doses (based on mg per kg body weight).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a sodium salt of celecoxib, which is significantly more soluble in water than presently-marketed neutral celecoxib. Due to the high pK_a of celecoxib (approximately 11), salts only form under strongly basic conditions. Typically, more than about one equivalent of a base is required to convert celecoxib to its salt form. A suitable aqueous solution for converting celecoxib to a salt has a pH of about 11.0 or greater, about 11.5 or greater, about 12 or greater, or about 13 or greater. Typically, the pH of such a solution is about 12 to about 13.

Salts of celecoxib are formed by reaction of celecoxib with an acceptable base. Acceptable bases include, but are not limited to, metal hydroxides and alkoxides. Metals include alkali metals (sodium, potassium, lithium, cesium), alkaline earth metals (magnesium, calcium), zinc, aluminum, and bismuth. Alkoxides include methoxide, ethoxide, n-propoxide, isopropoxide and t-butoxide. Additional bases include arginine, procaine, and other molecules having amino or guanidinium moieties with sufficiently high pK_a=s (e.g., pK_a=s greater than about 11, pK_a=s greater than about 11.5, or pK_a=s greater than about 12), along with compounds having a carbon-alkali metal bond (e.g., t-butyl lithium). Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base used to form a salt is typically about one or more, about two or more, about three or more, about four or more, about five or more, or about ten or more equivalents relative to celecoxib. Preferably, about three to about five equivalents of one or more bases are reacted with celecoxib to form a salt.

A celecoxib salt can be transformed into a second celecoxib salt by transmetallation or another process that replaces the cation of the first celecoxib salt. In one example, a sodium salt of celecoxib is prepared and is subsequently reacted with a second salt such as an alkaline earth metal halide (e.g., $MgBr_2$, $MgCl_2$, $CaCl_2$, $CaBr_2$), an alkaline earth metal

sulfate or nitrate (e.g., $Mg(NO_3)_2$, $Mg(SO_4)_2$, $Ca(NO_3)_2$, $Ca(SO_4)_2$), or an alkaline metal salt of an organic acid (e.g. calcium formate, magnesium formate, calcium acetate, magnesium acetate, calcium propionate, magnesium propionate) to form an alkaline earth metal salt of celecoxib.

In a preferred embodiment of the present invention, celecoxib salts are substantially pure. A salt that is substantially pure can be greater than about 80% pure, greater than about 85% pure, greater than about 90% pure, greater than about 95% pure, greater than about 98% pure, or greater than about 99% pure. Purity of a salt can be measured with respect to the amount of salt (as opposed to unreacted neutral celecoxib or base) or can be measured with respect to a specific polymorph, co-crystal, solvate, desolvate, hydrate, dehydrate, or anhydrous form of a salt.

A celecoxib salt of the present invention is generally significantly more soluble in water than presently-marketed neutral celecoxib, and is typically at least about three times, at least about five times, at least about ten times, at least about twenty times, at least about fifty times, or one at least about hundred times more soluble in water than celecoxib marketed by Pfizer Inc. and G. D. Searle & Co. (Pharmacia Corporation), such as celecoxib described at pages 2676-2680 and 2780-2784 of the 2002 edition of the Physicians= Desk Reference (hereinafter referred to as Apresently-marketed celecoxib@).

After dissolution, typically in an aqueous or partially-aqueous solution (e.g., where one or more polar organic solvents are a co-solvent), the salt can be neutralized by an acid or by dissolved gases such as carbon dioxide. Typically, the pH of such a solution is 11 or less, 10 or less, or 9 or less. Neutralizing the salt results in precipitation of an amorphous form of neutral celecoxib. Typically, neutralizing a celecoxib salt includes protonating the majority of negatively charged celecoxib anions, resulting in the formation of amorphous and/or metastable crystalline celecoxib, which are "neutral" (i.e., predominantly uncharged). Preferably, neutral celecoxib (including amorphous and metastable crystalline forms thereof) comprises 10% mol or less of charged celecoxib molecules. For example, at about pH 2 (e.g., about the pH of the stomach interior), solutions of the sodium salt of celecoxib precipitate immediately as an amorphous form of neutral celecoxib. The

amorphous form converts to a neutral metastable crystalline form, which subsequently becomes the stable, needle-like, insoluble form of neutral celecoxib. For example, amorphous neutral celecoxib formed from the sodium salt of Example 1 converts to metastable crystalline neutral celecoxib over about 5 to about 10 minutes. Amorphous neutral celecoxib can be characterized by a lack of a regular crystal structure, while metastable crystalline neutral celecoxib can be distinguished from typical crystalline neutral celecoxib by the PXRD pattern of isolated material.

Amorphous and metastable crystalline forms of neutral celecoxib are more soluble and likely more readily absorbed by a subject than stable crystalline forms of neutral celecoxib, because the energy required for a drug molecule to escape from a stable crystal is greater than the energy required for the same drug molecule to escape from a non-crystalline, amorphous form or a metastable crystalline form. However, the instability of neutral amorphous and neutral metastable crystalline forms makes them difficult to formulate as pharmaceutical compositions. As is described in U.S. Publication No. 2002/0006951, the teachings of which are incorporated herein by reference in their entirety, without stabilization by a crystallization inhibitor, such as a polymer, amorphous and metastable crystalline neutral celecoxib convert back to a stable, insoluble crystalline form of neutral celecoxib. The celecoxib salts of the present invention are stable, such that they can be formulated as pharmaceutical compositions and stored before administration to a subject. Only after dissolution and subsequent neutralization do celecoxib salts of the present invention precipitate as or transform into substantially amorphous neutral and then substantially metastable crystalline neutral forms. Preferably, dissolution and neutralization of celecoxib salts occur *in situ* in the gastrointestinal tract of a subject (e.g., stomach, duodenum, ileum), such that a maximal amount of amorphous and/or metastable crystalline neutral celecoxib is present after administration (e.g., *in vivo*), rather than before administration.

The length of time in which a celecoxib salt remains in solution and can be increased by adding one or more agents to the solution before precipitation occurs. Suitable agents include surfactants such as sodium dodecyl sulfate, polyethylene glycol (e.g., PEG 300, PEG 400), block co-polymers (e.g. Poloxamer 237) and polyoxyethylene

sorbitan esters (e.g., Tween 80). Other suitable surfactants are listed below. Additional agents that slow the rate of precipitation include polymers having amide, ester, ether, alcohol or ketone moieties. Preferably, the polymer includes one or more amide moieties, such as in polyvinylpyrrolidone. When one of the above-listed agents is added to a solution, the rate at which needles of neutral celecoxib appears is slowed. Polymers such as polyvinylpyrrolidone are particularly effective in retarding formation of neutral celecoxib crystals, as shown in Example 5, where no precipitation of celecoxib was observed for at least 10 minutes. While not being bound by theory, it is believed that polymers such as polyvinylpyrrolidone "trap" celecoxib salts as they dissolve, thereby inhibiting crystallization. Thus, the presence of such agents allows the formation of a supersaturated solution of a celecoxib salt and a high concentration of celecoxib will remain in solution for an extended period of time.

Celecoxib salts of the present invention are typically stable (i.e., more than 90% of the celecoxib salt does not change in composition or crystalline structure) for at least about one week, at least about one month, at least about two months, at least about three months, at least about six months, at least about nine months, at least about one year, or at least about two years at room temperature in the absence of moisture. Room temperature typically ranges from about 15°C to about 30°C. The absence of moisture, as defined herein, refers to celecoxib salts not contacting quantities of liquid, particularly water or alcohols. For purposes of the present invention, gases such as water vapor are not considered to be moisture.

The uptake of a drug by a subject can also be assessed in terms of maximum blood serum concentration and time to reach maximum blood serum concentration. Pharmaceutical compositions with a more rapid onset to therapeutic effect typically reach a higher maximum blood serum concentration (C_{max}) a shorter time after oral administration (T_{max}). Preferably, celecoxib salts of the present invention have a shorter T_{max} than presently-marketed celecoxib. Even more preferably, the therapeutic effects of celecoxib salts of the present invention begin to occur within about 30 minutes, within about 25 minutes, within about 20 minutes, within about 15 minutes, within about 10 minutes, or

within about 5 minutes of administration (e.g., oral administration). Ailments treatable with celecoxib and salts thereof of the present invention are discussed below. Treatment of pain is a preferred embodiment of the present invention.

While not being bound by theory, Applicants believe that the low solubility of presently-marketed celecoxib has an impact on other pharmaceutical properties. For example, the dose-response curve for presently-marketed celecoxib is nonlinear. Preferably, the dose-response curve for celecoxib salts of the present invention is linear or contains a larger linear region than presently-marketed celecoxib. Also, the absorption or uptake of presently-marketed celecoxib depends in part on food effects, such that uptake of celecoxib increases when taken with food, especially fatty food. Preferably, uptake of celecoxib salts of the present invention exhibits a decreased dependence on food, such that the difference in uptake of celecoxib salts when taken with food and when not taken with food is less than the difference in uptake of presently-marketed celecoxib.

A celecoxib salt of the present invention can be characterized by differential scanning calorimetry (DSC). The sodium salt of celecoxib prepared in Example 1 is characterized by at least 3 overlapping endothermic transitions between 50°C and 110°C (Fig. 1). Conditions for DSC can be found in Example 1.

Celecoxib salts of the present invention can be characterized by thermogravimetric analysis (TGA). The sodium salt of celecoxib prepared by Example 1 was characterized by TGA, and had about 3 loosely bound equivalents of water that evaporated between about 30°C and about 40°C, one more tightly bound equivalent of water that evaporated between about 40°C and about 100°C, and one very tightly bound equivalent of water that evaporated between about 140°C and about 160°C (Fig. 2). Conditions for TGA can be found in Example 1.

Celecoxib salts of the present invention can also be characterized by powder x-ray diffraction (PXRD). The sodium salt of celecoxib prepared by Example 1 had an intense reflection or peak at a 2-theta angle of 6.40°, and other reflections or peaks at 7.01°, 16.73°, and 20.93° (Fig. 3). Conditions for PXRD can be found in Example 1.

Celecoxib salts typically comprise solvate molecules and can occur in a variety of solvation states, also known as solvates. Thus, celecoxib salts of the present invention can

exist as crystalline polymorphs. Polymorphs are different crystalline forms of the same drug substance, and in the present use of the term include solvates and hydrates. For example, different polymorphs of a celecoxib salt can be obtained by varying the method of preparation (compare Examples 1 and 3). Crystalline polymorphs typically have different solubilities, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility.

Suitable solvate molecules include water, alcohols, other polar organic solvents, and combinations thereof. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol). Water is a preferred solvent. In a preferred embodiment, a celecoxib salt contains about 5 to about 6 equivalents or about 5.5 equivalents of water per equivalent of salt. In another preferred embodiment, a celecoxib salt contains about 3 to about 5 equivalents or about 4 equivalents of water per equivalent of salt, or about 1 to about 2 equivalents of water per equivalent of salt. Solvate molecules can be removed from a crystalline salt, such that the salt is either a partial or complete desolvate. If the solvate molecule is water (forming a hydrate), then a desolvated salt is said to be a dehydrate. A salt with all water removed is anhydrous. Solvate molecules can be removed from a salt by methods such as heating, treating under vacuum or reduced pressure, blowing dry air over a salt, or a combination thereof. Following desolvation, there are typically about one to about five equivalents, about one to about four equivalents, about one to about three equivalents, or about one to about two equivalents of solvent per equivalent of salt in a crystal.

A celecoxib salt of the present invention, in one of the above-listed forms, can co-crystallize with one or more other substances. The other substance or substances can be a salt, or can interact with a celecoxib salt through hydrogen bonds or other energetically-favorable manners.

Celecoxib salts of the present invention are prepared by contacting celecoxib with a solvent. Suitable solvents include water, alcohols, other polar organic solvents, and combinations thereof. Water and isopropanol are preferred solvents. Celecoxib is reacted with a base, where suitable bases are listed above, such that celecoxib forms a salt and preferably dissolves. Bases can be added to celecoxib with the solvent (i.e., dissolved in the solvent), such that celecoxib is solvated and deprotonated essentially simultaneously (see Example 3), or bases can be added after the celecoxib has been contacted with solvent (see Example 1). In the latter scenario, bases can either be dissolved in a solvent, which can be either the solvent already contacting celecoxib or a different solvent, can be added as a neat solid or liquid, or a combination thereof. Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base required is discussed above. The solvent can be evaporated to obtain crystals of the celecoxib salt, or the celecoxib salt may precipitate and/or crystallize independent of evaporation. Crystals of a celecoxib salt can be filtered to remove bulk solvent. Methods of removing solvated solvent molecules are discussed above.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colocorn™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of a celecoxib salt of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g.,

National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of metal salts of celecoxib.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of

Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of celecoxib from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to

about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of celecoxib typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers

(symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a metal salt of celecoxib; about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a an excipient which inhibits crystallization; and about 5% to about 50%, about 10% to about 40%, about 15% to about 35%, or about 30% to about 35% by weight of a binding agent. In one example, the weight ratio of the metal salt of celecoxib to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A celecoxib salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added,

for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein a celecoxib salt is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 25 mg to about 400 mg, and most preferably about 50 mg to about 200 mg.

Pharmaceutical compositions of the invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective amount that is preferably about 10 mg to about 1000 mg. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic or prophylactic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4)

of dose units, in a single administration provides a dose comprising a sufficient amount of the agent to result in the desired effect. Administration of such doses can be repeated as required, typically at a dosage frequency of 1 to about 4 times per day.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. A "subject" to which a celecoxib salt or a pharmaceutical composition thereof can be administered includes a human subject of either sex and of any age, and also includes any nonhuman animal, particularly a warm-blooded animal, more particularly a domestic or companion animal, illustratively a cat, dog or horse. When the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib (measured as the neutral form of celecoxib, that is, not including counterions in a salt or water in a hydrate) relatively low in the preferred range of about 10 mg to about 1000 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of celecoxib is likely to require dose units containing a relatively greater amount of celecoxib.

Typical dose units in a pharmaceutical composition of the invention contain about 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg. Other doses that are not in current use for Celebrex™ may become preferred, if the bioavailability is changed with a novel formulation. For instance, 300 mg may become a preferred dose for certain indications.

A dose unit containing a particular amount of celecoxib can be selected to accommodate any desired frequency of administration used to achieve a desired daily dosage. The daily dosage and frequency of administration, and therefore the selection of appropriate dose unit, depends on a variety of factors, including the age, weight, sex and medical condition of the subject, and the nature and severity of the condition or disorder, and thus may vary widely.

For pain management, pharmaceutical compositions of the present invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a pharmaceutical composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is immediately swallowed. Thus, "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, ileum and colon. The term "orally deliverable" herein means suitable for oral administration.

Pharmaceutical compositions of the invention are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such pharmaceutical compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional non-steroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, pharmaceutical compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and

possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in subjects with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in subjects prior to surgery or subjects taking anticoagulants.

Contemplated pharmaceutical compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such pharmaceutical compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendonitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Pharmaceutical compositions of the present invention are useful to treat gastrointestinal conditions such as, but not limited to, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such pharmaceutical compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

In addition, these pharmaceutical compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Also, such pharmaceutical compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

The pharmaceutical compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such pharmaceutical compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Further, pharmaceutical compositions of the present invention are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, bums, and trauma following surgical and dental procedures.

The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a pharmaceutical composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the

disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

The present pharmaceutical compositions can be used in combination with other therapies or therapeutic agents, including but not limited to, therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, GABA active agents, norexin neuropeptide modulators, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, alpha-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene,

ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, modafinil, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsahnide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, topiramate, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to

Ther-3 and Ther-12 (Analgesic (D)ental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Non-steroidal)).

Pharmaceutical compositions of the present invention are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

These pharmaceutical compositions are also useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such pharmaceutical compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Moreover, pharmaceutical compositions of the present invention are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell

cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer; pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such pharmaceutical compositions can also be used to treat fibrosis that occurs with radiation therapy. These pharmaceutical compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, pharmaceutical compositions of the present invention can be used to prevent polyps from forming in subjects at risk of FAP.

Also, the pharmaceutical compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (i.e., treatment of osteoporosis), and for treatment of glaucoma.

Preferred uses for pharmaceutical compositions of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention. A particular preferred use is for rapid pain management, such as when a celecoxib salt or a pharmaceutical composition thereof is effective in treating pain within about 30 minutes or less.

Besides being useful for human treatment, pharmaceutical compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, pharmaceutical compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

EXEMPLIFICATION

Example 1

Celecoxib sodium salt from aqueous solution

To 77.3 mg of commercially-available celecoxib was added 1.0 mL distilled water, followed by 0.220 mL of 1 M NaOH (VWR). The mixture was heated with stirring to 60°C, whereupon an additional 1.0 mL distilled water was added. Solid NaOH (22 mg) was added, and the solid NaOH and celecoxib dissolved. The mixture was heated again at 60°C to evaporate water. About 15 mL reagent-grade ethanol was added, while the mixture was stirred and heated at 60°C with air blowing over the solution. Heating continued until the solution was dry. The resulting material was analyzed by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), the results of which are seen in Figs. 1-3. The product was found to contain about 5.5 equivalents of water per equivalent of salt.

DSC analysis of the salt sample prepared above was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (®2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (®2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing 2.594 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was 20°C with a heating rate of 10°C/minute, and the ending temperature was 200°C. The resulting DSC analysis is shown in Fig. 1.

TGA analysis of the salt sample prepared above was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses

Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (®2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (®2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing 2.460 mg of sample in a platinum pan. The starting temperature was 20°C with a heating rate of 10□C/minute, and the ending temperature was 300°C. The resulting TGA analysis is shown in Fig. 2.

A powder X-ray diffraction pattern for the salt sample prepared above was performed using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0 (®1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((®1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a Kα line at 1.5406Å; x-y stage was manual; collimator size was 0.3 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The PXRD pattern for the compound prepared above is shown in Fig. 3. In the diffractogram of Fig. 3, the background has been removed.

Example 2

Celecoxib sodium salt from 2-propanol solution

To 126.3 mg of celecoxib (Fako Hazlari) was added a 1.0 mL aliquot of isopropanol, and the mixture was heated to dissolve the celecoxib. Sodium ethoxide was added as a solution 21% in ethanol (0.124 mL solution, 3.31×10^{-4} mol sodium ethoxide). An additional 1.0 mL of isopropanol was added. The mixture was stirred to obtain a slurry of white crystalline solids that appeared as fine birefringent needles by polarized light microscopy.

The slurry was filtered by suction filtration and rinsed with 2 mL of isopropanol. The solid was allowed to air dry before being gently ground to a powder. The product was analyzed by PXRD, DSC, and TGA as in Example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The compound lost 17.35% weight between room temperature and 120°C. The DSC trace shows a broad endothermic region, which is consistent with a loss of volatile components with increasing temperature. The endotherm peaks at 66°C. The PXRD pattern has characteristic peaks including, but not limited to, 2-theta angles of 4.09°, 4.99°, 6.51°, 9.99°, and 11.59°.

Example 3

Celecoxib sodium salt tetrahydrate from aqueous solution

Synthesis 1: To a vial was added 29.64 mg celecoxib and 3.00 mL of 1 N sodium hydroxide. The celecoxib dissolved immediately. After a time, the celecoxib precipitated from solution.

Synthesis 2: To a vial was added 7.10 mg celecoxib and 3.00 mL of 1 N sodium hydroxide. The celecoxib dissolved. Overnight, the celecoxib precipitated and formed white, needle-like crystals.

Synthesis 3: To a vial was added 17.6 mg celecoxib and 10 mL of 1 N sodium hydroxide. The celecoxib dissolved. The vial was placed in a beaker wrapped in aluminum foil and filled with a large tissue for insulation. The beaker was left and crystals formed within about 12-36 hours.

Analysis: The product solids from syntheses 1 and 2 were combined and analyzed by PXRD, DSC, and TGA as in example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The product salt was found to contain about 4 equivalents of water per equivalent of salt. TGA showed a weight loss of 14.9% as the temperature was increased from room temperature to 100°C at 10°C/min. DSC analysis showed a large endothermic transition at 74+/-1.0°C and a second broad and noisy endothermic transition at about 130-5.0°C. The PXRD pattern has characteristic peaks including, but not limited to, 2-theta angles of 3.6°, 8.9°, 9.6°, 10.8°, 11.4°, and 20.0°.

Example 4

Pharmacokinetic Studies in Rats

The sodium salt hydrate form (from Example 6) was compared with Celebrex powder in terms of absorption in rats (Figs. 4A and 4B).

Pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt form are shown in Figs. 4A and 4B. Solids were placed in size 9 gelatin capsules (Torpac) and dosed via gavage needle, followed by oral gavage of 1 mL water. Celebrex® granulation was transferred from commercial 200 mg capsules. The sodium salt was blended with Povidone K30 (4:1 weight ratio to the sodium salt of celecoxib). The plots are averages of plasma levels at each of the timepoints from plasma of 5 rats.

The pharmacokinetics at 5 mg/kg doses of celecoxib or the celecoxib sodium salt demonstrate a faster peak level of the drug in plasma. Early timepoints show higher levels

of celecoxib in plasma from the sodium salt relative to Celebrex® (in particular, see Figure 4A).

Example 5

Solubility of Celecoxib Sodium in the Presence of Polyvinylpyrrolidone

Water was added to a 1:4 mixture of celecoxib sodium and polyvinylpyrrolidone to obtain a clear solution. The solution was stable for at least 15 minutes, after which time crystals of neutral celecoxib began to form.

Crystalline neutral celecoxib did not dissolve when added to aqueous polyvinylpyrrolidone or when water was added to a dry blend of neutral crystalline celecoxib and polyvinylpyrrolidone.

Example 6

Preparation of Celecoxib Sodium

The free acid of Celecoxib (5.027 g) was suspended in an aqueous solution of NaOH (13.181 mL, 1 M). The suspension was gently heated at 60^{O}C for 1 minute to dissolve the remaining solid. The mixture was allowed to cool to room temperature, which yielded no precipitation. Further cooling in an ice bath for 1 hour gives precipitation of the product. The resulting solution was filtered and allowed to air dry.

Characterization of the product has been achieved via TGA, DSC, PXRD, Raman spectroscopy, microscopy, and ^{1}H NMR spectroscopy. NMR acquisitions were performed on a Varian 300 MHz Spectrometer in (methyl sulfoxide)-d^{6}.

Example 7

The celecoxib salt of prepared by the methods of Example 6 was administered to dogs and compared to administration of commercially available celecoxib.

Six male beagle dogs aged 2-4 years old and weighing 8-12 kg. were food-deprived. The dogs were given water. Each of the dogs was administered 3 test doses as described below and allowed a one week washout period between doses. The test doses were: (1) commercially available celecoxib in the form of Celebrex ® at 1 milligrams per kilograms (mpk) combined with 70/30 PEG400/water which was administered IV, (2) oral dose of commercially available celecoxib in the form of Celebrex ® at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules and (3) oral dose of the sodium salt of the instant invention as prepared according to Example 6 at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules. Blood samples of approximately 2 ml in sodium heparin were obtained by jugular venipuncture at 0.25, 0.5, 1, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples were obtained predose and at 0.08 hr for the IV study. Blood samples were immediately placed on ice and centrifuged within 30 min of collection at 3200 g at 4 oC nominal for 10 minutes. Plasma samples (~1.0 ml) were harvested and stored in 4 aliquots of 0.25 ml at -20 oC. Plasma samples were analyzed for celecoxib using a LC-MS/MS assay with a lower limit of quantitation of 5 ng/ml. Pharmacokinetic profiles of celecoxib in plasma wer analyzed using the PhAST software Program (Version 2.3, Pheonix Life Sciences, Inc.). The absolute biovavailability (F) is reported for oral doses relative to the IV dose.

Example 8

Celecoxib-Lithium Salt Preparation Method: MO-116-49B

To 100mg of commercially available Celecoxib was added 0.35M LiOH(aq) (Lithium Hydroxide Monohydrate – Aldrich Cat#25,427-4, Lot 00331K1) solution with a Lithium:celecoxib ratio of 1.53:1 in a vial with a Teflon coated silicon rubber septum cap. The mixture was gently heated during dissolution with occasional swirling until all solids dissolved. Flowing dry nitrogen was blown over the solution for 2 days through stainless steel needles inserted into the septum cap until the solution was dry. Characterization of the product was achieved via DSC (Fig. 14), TGA (Fig. 15), Raman spectroscopy (Fig. 16) and PXRD (Fig. 17).

Unless specifically stated, all equipment and instrumentation used for analysis is the

same as in Examples 1-6.

Celecoxib-Lithium Salt Data (DSC)

1.56mg of collected sample was placed into an aluminum DSC pan with cover. The DSC pan was sealed with crimping and placed in TA Instruments Q1000 DSC. The sealed pan was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. Figure 14 is the resulting DSC analysis.

Celecoxib-Lithium Salt Data (TGA)

8.2290mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA. The pan was heated 10°C/min to 300°C with 40ml/min nitrogen purge gas. The results of the TGA are depicted in Fig. 15.

Celecoxib-Lithium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 μm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results of the Raman spectroscopy are depicited in Fig. 16.

Celecoxib-Lithium Salt Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube.. The tube was placed into a Rigaku D/Max Rapid PXRD and set to: Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes.

Example 9

Celecoxib-Potassium Salt: Preparation Method MO-116-49A

100mg of Celecoxib (Fako Ilaclari A,S,) was dissolved in a 0.35M KOH(aq) solution (Potassium Hydroxide – Spectrum, Cat# P0180, Lot#PN0690) with a Potassium:Celecoxib ratio of 1.40:1 in a vial with a Teflon coated silicon rubber septum cap. The resulting solution was gently warmed during dissolution with occasional swirling until all solids dissolved. After all solids were dissolved, the solution was dried by flowing dry nitrogen over the solution for 2 days through stainless steel needles inserted into the septum cap. Analysis of the resulting product was performed. Characterization of the product was achieved via DSC (Fig. 18,) TGA (Fig. 19), Raman spectroscopy (Fig. 20) and PXRD (Fig. 21).

Celecoxib-Potassium Salt (MO-116-49A) Data (DSC)

1.119 mg of collected sample was placed into an aluminum DSC pan with cover. The pan was sealed with crimping and placed into a TA Instruments Q1000 DSC. The DSC was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. The results are depicted in the graph of Fig. 18.

Celecoxib-Potassium Salt (MO-116-49A) Data (TGA)

5.9890 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 19.

Celecoxib-Potassium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collections. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 µm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results are depicted in Fig. 20.

Celecoxib-Potassium Salt (MO-116-49A) Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 21.

Example 10

Celecoxib-Potassium Salt: Preparation Method MO-116-55D

An alternative method of preparing a celecoxib-potassium salt of the instant invention was performed. 100mg of celecoxib (commercially available) was dissolved in 2.2mL toluene and 0.1mL methanol in a vial with a Teflon® coated silicon rubber septum cap. The solution was warmed gently during dissolution with occasional swirling until all solids were dissolved. 1.03 equivalents of KOH (Potassium Hydroxide – Spectrum, Cat#

P0180, Lot#PN0690) using a 3M KOH(aq) solution were added to the solution. After the resulting phase separation, the bottom phase was removed and was dried by flowing dry nitrogen over the solution for 1 day through stainless steel needles inserted into the septum cap.

Analysis was performed. Characterization of the product was achieved via TGA (Fig. 22), Raman spectroscopy (Fig. 23) and PXRD (Fig. 24).

Celecoxib-Potassium Salt (MO-116-55D) Data (TGA)

5.4470 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 22.

Celecoxib-Potassium Salt (MO-116-55D) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters of the spectrometer were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 µm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results are depicted in Fig. 23.

Celecoxib-Potassium Salt (MO-116-55D) Data (PXRD)

A small amount of collected sample was placed in a 0.3 mm glass PXRD tube. The

tube was placed into a Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 24.

Example 11

Celecoxib-Calcium Salt: Preparation Method MO-116-62A

100mg of celecoxib (commercially available) was dissolved in a 1M NaOH methanol solution at a 1:1 ratio of NaOH:Celecoxib in a vial and heated gently with occasional swirling until all solids were dissolved. 3M $CaCl_2$ in methanol was added to achieve a ratio of 1.5:1 Ca^{2+} to Celecoxib. The precipitate was filtered with a centrifuge tube filter (Corning Inc. Costar (0.22 micron) #8169) in an Eppendorf Centrifuge (5415D) set at 12000 rpm for 5 minutes. The upper section of the Eppendorf tube containing the solids was placed into a vial with a rubber septum cap. The powder was dried overnight by flowing dry nitrogen into the vial through stainless steel needles inserted in the septum cap. Analysis was performed. Characterization of the product was achieved via TGA (Fig. 25), Raman spectroscopy (Fig. 26) and PXRD (Fig. 27).

Celecoxib-Calcium Salt (MO-116-62A) Data (TGA)

3.4140 mg of collected sample was placed into a platinum TGA pan. The pan was place in TA Instruments Q500 TGA and heated 10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas.

Celecoxib-Calcium Salt (MO-116-62A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans.

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 µm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

Celecoxib-Calcium Salt (MO-116-62A) Data (PXRD)

A small amount of collected sample was placed into a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to15 minutes.

Example 12

To aid in the analysis of some of the data retrieved, commercially available celecoxib was subjected to the same analytical techniques of particle-induced X-ray diffraction (PXRD) and Raman spectroscopy. The results were used as a comparison for the salts of the instant invention.

Comparison Data: Celecoxib (PXRD)

A small amount of commercially available celecoxib was placed in a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 28.

Comparison Data: Celecoxib (Raman)

A small quantity of commercially available celecoxib was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was

set to 6 background scans and 12 sample collection. The parameters were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 µm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results are depicted in Fig. 29.

Example 13

Co-crystals of celecoxib and nicotinamide were prepared. 100 mg. o f 0.26 mmol celecoxib (MW 381.4 g/mol) and 32.0 mg of 0.26 mmol. nicotinamide (MW 122. g/mol) were each dissolved in 2 mL acetone (MW 58.1 g/mol). The two solutions were mixed and the resulting mixture was allowed to evaporate slowly overnight. The precipitated solid was collected and characterized using powder diffraction, DSC, Raman spectroscopy, IR and TGA (data not shown).

A portion of the powder was tested using DSC. The resulting DSC melting curve showed a sharp endotherm at 117.05 °C

A portion of the powder was also tested using PXRD. The PXRD showed peaks unique to the co-crystal which are: 3.770, 7.330, and 13.89. The data indicated other peaks that may be unique but may also be contamination from either pure celecoxib or nicotinamide are: 5.550, 9.690, 11.05, 13.01, 15.99, and 16.59.

Example 14

A celecoxib and saccharin co-crystal was prepared using the following materials:

Compound	Stock Concentration (mg/ mL)	Molecular Weight (g/mol)	Amount (mg, µL)	Moles (mmol)
Celecoxib	65	381.4	10, 154	0.026
Saccharin	5	183.19	4.76, 95	0.026
Acetone	----	58.1	400 µL	-----

Stock solutions containing 65 mg/mL and 5mg/mL of celecoxib and saccharin from methanol, respectively, were prepared. Celecoxib (10 mg, 154 µL, 0.026 mmol) and saccharin (4.76 mg, 95 µL, 0.026 mmol) were dispensed into a 1 mL glass vial. The solvent was evaporated and the remaining solid was dried for 10 min. The solid was dissolved in acetone (400 µL) and was left to evaporate slowly overnight. Thin needle-like crystals were observed along the side of the vial and were collected and characterized using powder diffraction, DSC, Raman spectroscopy and TGA.

The results are depicted in Fig. 30 (DSC), Fig. 31 (TGA), Fig. 32 (Raman Shift), fig. 33 is PXRD powder pattern of the co-crystal Figs. 34 through 40 are comparative data.

DSC data (Fig. 30) shows an endotherm at 148.9 °C followed by recrystallization and melting at 157.3 °C. TGA (Fig. 31) shows decomposition of the product beginning at approximately 195 °C. The DSC and raman data and powder pattern are distinct from either starting material (see Figs33 to 40).

Example 15

A propylene glycol solvates of the sodium salt of celecoxib was prepared. To a solution of celecoxib (312 mg; 0.818 mmol) in Et_2O (6 mL) was added propylene glycol (0.127 ml, 1.73 mmol). To the clear solution was added NaOEt in EtOH (21%, 0.275 µL, 0.817 mmol). After 1 minute, crystals began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The off-white solid was then air-dried and collected. This was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 41 and 42.

Example 16

A propylene glycol solvate of the potassium salt of celecoxib was prepared. To a solution of celecoxib (253 mg, 0.664 mmol) in Et_2O (6 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added KO*t*Bu in THF (1 M, 0.66 mL, 0.66 mmol). Crystals immediately began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. This solid was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 43 and 44.

Example 17

A propylene glycol solvate of lithium salt of celecoxib was prepared. To a solution of celecoxib (264 mg, 0.693 mmol) in Et_2O (8 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added *t*Bu-Li in pentane (1.7 M, 0.40 mL, 0.68 mmol). A brown solid formed immediately but dissolved within one minute yielding white solid. The white solid crystallized completely after 10 minutes. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. The solid was a 1:1 solvate. The solid was characterized by TGA and the results are depicted in Fig. 45.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A composition comprising a crystalline metal salt of celecoxib, wherein said salt is substantially more soluble in water than neutral celecoxib.

2. The composition of Claim 1, wherein the salt transforms or converts into an amorphous neutral celecoxib after contacting acidic, neutral, or weakly basic solution.

3. The composition of Claim 2, wherein the amorphous neutral celecoxib transforms or converts into a metastable crystalline neutral celecoxib.

4. The composition of Claim 3, wherein the metastable crystalline neutral celecoxib transforms or converts into a stable crystalline neutral celecoxib.

5. The composition of Claim 1, wherein said composition is suitable for oral delivery.

6. The composition of Claim 1, wherein said salt is an alkali metal salt of celecoxib.

7. The composition of Claim 6, wherein said salt is a potassium salt of celecoxib.

8. The composition of Claim 6, wherein said salt is a sodium salt of celecoxib.

9. The composition of Claim 1, wherein said salt is an alkaline earth metal, zinc, or aluminum salt of celecoxib.

10. The composition of Claim 8, wherein said salt is characterized by at least 3 overlapping endothermic transitions observed by differential scanning calorimetry between 50°C and 110°C.

11. The composition of Claim 8, wherein said salt comprises about 3 equivalents of water per equivalent of salt that are lost upon heating to about 30°C to about 40°C, about 1 equivalent of water per equivalent of salt that is lost upon further heating to about 40°C to about 100°C, and about 1 equivalent of water per equivalent of salt that is lost upon further heating to about 140°C to about 160°C.

12. The composition of Claim 6, wherein said salt comprises solvate molecules.

13. The composition of Claim 12, wherein the solvate molecules are water.

14. The composition of Claim 13, wherein said salt is greater than about 80% pure.

15. The composition of Claim 14, wherein said salt is greater than about 90% pure.

16. The composition of Claim 12, wherein the solvate molecules are alcohols.

17. The composition of Claim 16, wherein the alcohol is selected from the group consisting of methanol, ethanol, n-propanol, and isopropanol.

18. A composition comprising a polymorph of the salt of Claim 6.

19. A composition comprising a polymorph of the salt of Claim 8.

20. The composition of Claim 19, wherein said polymorph contains about 5 to about 6 equivalents of water per equivalent of salt.

21. The composition of Claim 19, wherein said polymorph contains about 3 to about 5 equivalents of water per equivalent of salt.

22. The composition of Claim 6, wherein said salt is partially or completely desolvated.

23. The composition of Claim 22, wherein said salt is partially or completely dehydrated.

24. A sodium salt of celecoxib, wherein said salt is characterized by a powder X-ray diffraction spectrum having peaks at 2-theta angles of 6.4°, 7.0°, 16.7°, and 20.9°.

25. A sodium salt of celecoxib, wherein said salt is characterized by a powder X-ray diffraction spectrum having peak at 2-theta angles of 4.1°, 5.0°, 6.5°, 10.0°, and 11.6°.

26. A sodium salt of celecoxib, wherein said salt is characterized by a powder X-ray diffraction spectrum having peak at 2-theta angles of 3.6°, 8.9°, 9.6°, 10.8°, 11.4°, and 20.0°.

27. A metal salt of celecoxib, wherein said salt is prepared by a process comprising the steps of:

a. contacting celecoxib with a solvent;

b. reacting celecoxib with greater than one equivalent of one or more metal containing bases, such that celecoxib dissolves; and

c. removing said solvent, thereby obtaining crystals of said metal salt of celecoxib.

28. The salt of Claim 27, wherein the solvent is water or an alcohol.

29. The salt of Claim 28, wherein the base is alkali metal or alkaline earth metal hydroxide or alkoxide.

30. The salt of Claim 29, wherein the base of step (b) is sodium hydroxide or sodium ethoxide.

31. The salt of Claim 30, wherein the base of step (b) is dissolved in the solvent of step (a).

32. A method of preparing a metal salt of celecoxib, said method comprising the steps of:

b. contacting celecoxib with a solvent;

c. reacting celecoxib with greater than one equivalent of one or more metal containing bases, such that celecoxib dissolves; and

d. removing said solvent, thereby obtaining crystals of said metal salt of celecoxib.

33. The method of Claim 32, wherein the base is alkali metal or alkaline earth metal hydroxide or alkoxide.

34. The method of Claim 33, wherein the base is sodium hydroxide or sodium ethoxide.

35. The method of Claim 34, wherein the base of step (b) is dissolved in the solvent of step (a).

36. A method of treating a subject suffering from pain comprising administering to said subject a salt of celecoxib, wherein said salt is substantially more soluble in water than neutral celecoxib and wherein said salt reduces pain within 30 minutes.

37. The method of Claim 36, wherein the salt is administered to the subject orally.

38. The method of Claim 36, wherein the salt is used in combination with other therapies.

39. The method of Claim 37, wherein said salt is a metal salt of celecoxib.

40. The method of Claim 39, wherein said salt is an alkali metal salt of celecoxib.

41. The method of Claim 40, wherein said salt is a potassium salt of celecoxib.

42. The method of Claim 40, wherein said salt is a sodium salt of celecoxib.

43. The method of Claim 42, wherein the salt is a hydrate.

44. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a metal salt of celecoxib, wherein said salt is substantially more soluble in water than neutral celecoxib.

45. The pharmaceutical composition of Claim 44, wherein said pharmaceutical composition is suitable for oral administration.

46. The pharmaceutical composition of Claim 44, wherein the pharmaceutical composition further comprises a second therapeutic agent.

47. The pharmaceutical composition of Claim 44, wherein said salt is an alkali metal salt of celecoxib.

48. The pharmaceutical composition of Claim 47, wherein said salt is a potassium salt of celecoxib.

49. The pharmaceutical composition of Claim 47, wherein said salt is a sodium salt of celecoxib.

50. The pharmaceutical composition of Claim 49, wherein said salt is greater than about 80% pure.

51. The pharmaceutical composition of Claim 50, wherein said salt is greater than about 90% pure.

52. The pharmaceutical composition of Claim 51, wherein the salt is a hydrate.

53. The pharmaceutical composition of Claim 53, wherein the crystallization inhibiting carrier or diluent is a polymer comprising one or more amide, ester, ketone, alcohol or ether functional groups.

54. The pharmaceutical composition of Claim 53, wherein the amide, ester, ketone, alcohol or ether functional groups are pendant groups on the polymer.

55. The pharmaceutical composition of Claim 54, wherein the polymer comprises one or more amide functional groups.

56. The pharmaceutical composition of Claim 55, wherein the polymer is polyvinylpyrrolidone.

57. The pharmaceutical composition of Claim 55, further comprising a solid organic acid.

58. The pharmaceutical composition of Claim 57, wherein the solid organic acid is tartaric acid.

59. A pharmaceutical composition comprising a surfactant and a salt of celecoxib.

60. The pharmaceutical composition of Claim 59, wherein the surfactant is selected from the group consisting of sodium dodecyl sulfate, polyethylene glycol and polyoxyethylene sorbitan esters.

61. A method of retarding the formation of neutral celecoxib crystals in a solution of a sodium salt of celecoxib, comprising the steps of:

a) contacting said salt with a polymer comprising one or more amide, ester, ether, alcohol or ketone functional group; and

b) dissolving said salt in an aqueous solution.

62. The method of Claim 61, wherein step (a) occurs prior to step (b).

63. The method of Claim 61, wherein step (a) and step (b) occur simultaneously.

64. The method of Claim 61, wherein the polymer comprises one or more amide functional groups.

65. The method of Claim 64, wherein the polymer is polyvinylpyrrolidone.

66. A method of treating a subject suffering from inflammation comprising administering to said subject a salt of celecoxib, wherein said salt is substantially more soluble in water than neutral celecoxib.

67. A method of treating a subject suffering from cancer comprising administering to said subject a salt of celecoxib, wherein said salt is substantially more soluble in water than neutral celecoxib.

68. A pharmaceutical composition comprising a metal salt of celecoxib, wherein said metal salt of celecoxib is neutralized upon contact with water and forms an amorphous neutral celecoxib, an excipient which solubilizes said metal salt of celecoxib, and an excipient which inhibits said crystallization of the amorphous neutral celecoxib.

69. The pharmaceutical composition of Claim 68, wherein the rate of crystallization is inhibited as compared to amorphous neutral celecoxib alone.

70. The pharmaceutical composition of Claim 68, wherein crystallization occurs when amorphous neutral celecoxib converts to metastable neutral crystalline celecoxib or stable neutral crystalline celecoxib.

71. The pharmaceutical composition of Claim 68, wherein contact with water occurs in the gastrointestinal tract.

72. The pharmaceutical composition of Claim 68, wherein the pharmaceutical composition is intended for oral administration.

73. The pharmaceutical composition of Claim 68, wherein the metal salt of celecoxib is an alkali metal salt of celecoxib.

74. The pharmaceutical composition of Claim 73, wherein the alkali metal salt of celecoxib is a sodium salt of celecoxib.

75. The pharmaceutical composition of Claim 73, wherein said excipient which solubilizes said metal salt of celecoxib is amphiphilic or comprises one or more amphiphilic moieties.

76. The pharmaceutical composition of Claim 75, wherein said excipient which solubilizes said metal salt of celecoxib, is an amphiphilic polymer or comprises an amphiphilic polymer.

77. The pharmaceutical composition of Claim 76, wherein the amphiphilic polymer is a polyalkylene glycol.

78. The pharmaceutical composition of Claim 77, wherein the polyalkylene glycol comprises one or more ethylene glycol or propylene glycol repeat units or a combination thereof.

79. The pharmaceutical composition of Claim 78, wherein the polyalkylene glycol is esterified.

80. The pharmaceutical composition of Claim 76, wherein the excipient which solubilizes said metal salt of celecoxib is selected from the group consisting of a poloxamer, a polyalkylene glycolated ester of tocopherol, and a macrogolglyceride.

81. The pharmaceutical composition of Claim 80, wherein the excipient which solubilizes said metal salt of celecoxib is selected from the group consisting of Poloxamer 237, d-alpha-tocopherol polyethylene glycol-1000 succinate and stearoyl macrogol-32 glycerides.

82. The pharmaceutical composition of Claim 76, wherein said excipient which inhibits crystallization is a binding agent.

83. The pharmaceutical composition of Claim 82, wherein the binding agent is a cellulose.

84. The pharmaceutical composition of Claim 83, wherein the cellulose is hydroxypropylmethylcellulose or hydroxypropylmethylcellulose.

85. The pharmaceutical composition of Claim 84, wherein the cellulose is hydroxypropylcellulose.

86. The pharmaceutical composition of Claim 84, wherein said pharmaceutical composition comprises about 10% to about 50% by weight of the metal salt of celecoxib, about 10% to about 50% by weight of the excipient which solubilizes said metal salt of celecoxib, and about 5% to about 50% by weight of the binding agent.

87. The pharmaceutical composition of Claim 86, wherein said pharmaceutical composition comprises about 25% to about 50% by weight of the metal salt of celecoxib, about 25% to about 50% by weight of the excipient which solubilizes said metal salt of celecoxib, and about 10% to about 40% by weight of the binding agent.

88. The pharmaceutical composition of Claim 87, wherein said pharmaceutical composition comprises about 30% to about 45% by weight of the metal salt of celecoxib, about 30% to about 45% by weight of the excipient which solubilizes

said metal salt of celecoxib, and about 15% to about 35% by weight of the binding agent.

89. The pharmaceutical composition of Claim 88, wherein said pharmaceutical composition comprises about 30% to about 35% by weight of the metal salt of celecoxib, about 30% to about 35% by weight of the excipient which solubilizes said metal salt of celecoxib, and about 30% to about 35% by weight of the binding agent.

90. A pharmaceutical composition comprising a sodium salt of celecoxib, d-alpha-tocopherol polyethylene glycol-1000 succinate, and hydroxypropylcellulose.

91. The pharmaceutical composition of Claim 90, wherein said pharmaceutical composition comprises 10% to 50% by weight of the sodium salt of celecoxib, 10% to 50% by weight of d-alpha-tocopherol polyethylene glycol-1000 succinate, and 5% to 50% by weight of hydroxypropylcellulose.

92. The pharmaceutical composition of Claim 91, wherein said pharmaceutical composition comprises 30% to 45% by weight of the sodium salt of celecoxib, 30% to 45% by weight of d-alpha-tocopherol polyethylene glycol-1000 succinate, and 15% to 35% by weight of hydroxypropylcellulose.

93. The pharmaceutical composition of Claim 92, wherein said pharmaceutical composition comprises 30% to 35% by weight of the sodium salt of celecoxib, 30% to 35% by weight of d-alpha-tocopherol polyethylene glycol-1000 succinate, and 30% to 35% by weight of hydroxypropylcellulose.

94. A method of treating a subject suffering from pain comprising administering to said subject a pharmaceutical composition comprising a sodium salt of celecoxib, d-alpha-tocopherol polyethylene glycol-1000 succinate, and hydroxypropylcellulose.

95. The method of Claim 94, further comprising administering to said subject caffeine.

96. The method of Claim 94, wherein the pharmaceutical composition is administered orally.

97. A method of treating a subject suffering from inflammation comprising administering to said subject a pharmaceutical composition comprising a sodium salt of celecoxib, d-alpha-tocopherol polyethylene glycol-1000 succinate, and hydroxypropylcellulose.

98. A method of treating a subject suffering from cancer comprising administering to said subject a pharmaceutical composition comprising a sodium salt of celecoxib, d-alpha-tocopherol polyethylene glycol-1000 succinate, and hydroxypropylcellulose.

99. A co-crystal comprising celecoxib and saccharin.

100. A co-crystal comprising celecoxib and nicotinamide.

CRYSTALLINE SALTS OF CELECOXIB

ABSTRACT OF THE DISCLOSURE

Celecoxib is a non-steroidal anti-inflammatory drug that selectively inhibits cyclooxygenase II, which allows celecoxib to have fewer side effects in subjects. However, celecoxib is poorly soluble in water, leading to a slow uptake from the gastrointestinal tract, such that orally-administered celecoxib is not optimally useful in rapid pain management. Celecoxib salts of the present invention, particularly a sodium salt, have been found to have substantially increased water solubility and exhibit a more rapid peak in plasma concentration after administration, as compared to presently-marketed celecoxib.

FIG. 1

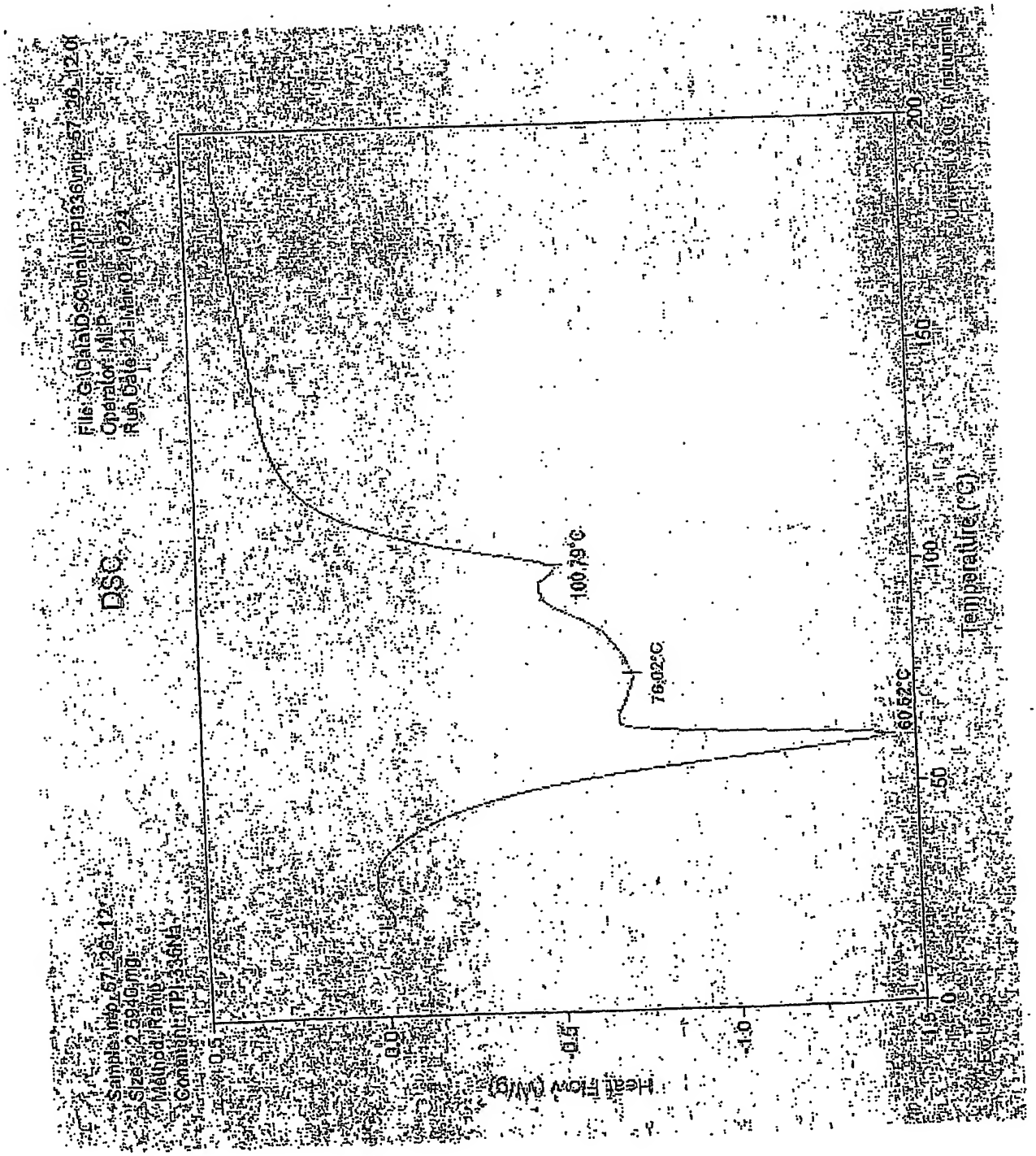

DSC
100.79°C
76.02°C
60.52°C
Temperature (°C)
Heat Flow (W/g)
Exo Up
Universal V3.9A TA Instruments
File: C:\Data\DSC\small\TP336mlp-57_26_12.01
Operator: MLP
Run Date: 2-Jan-02 16:23
Sample: mlp-57_26_12
Size: 2.5940 mg
Method: Ramp
Comment: TP-336Na

FIG. 2

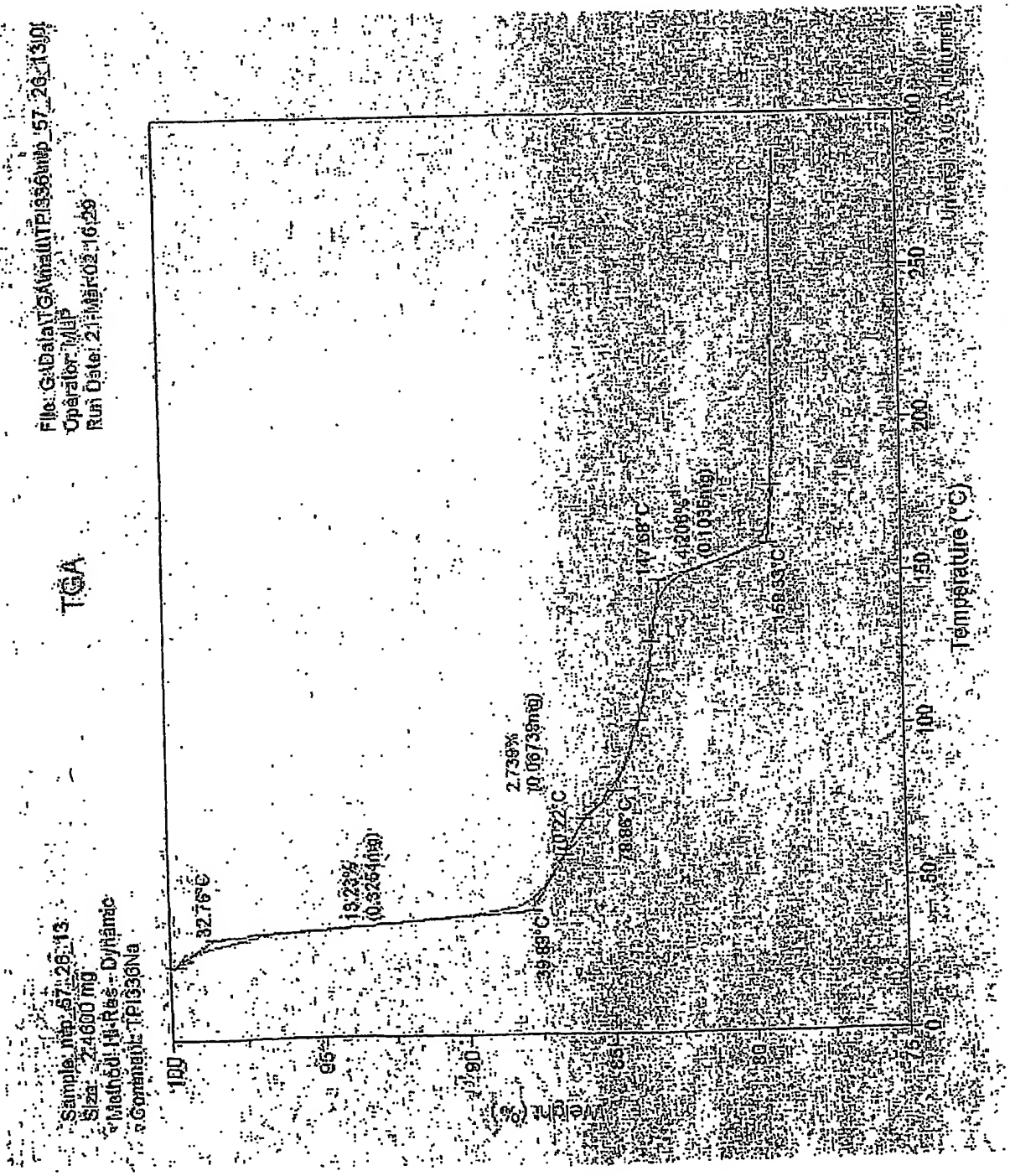
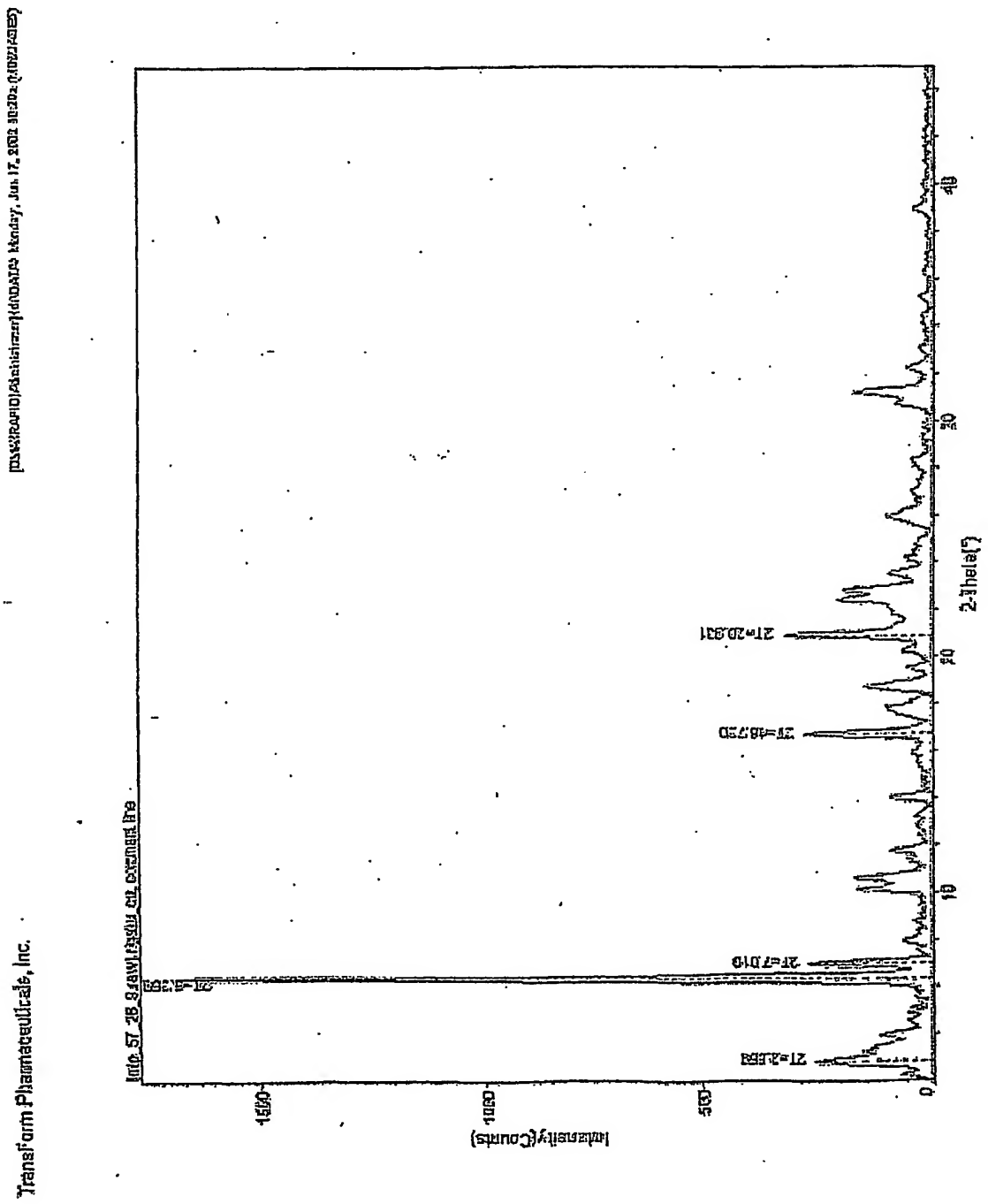

File: G:\Data\TGA\small\TP1336mlp 57_26_13.01
Operator: MP
Run Date: 21-Mar-03 16:29
TGA
Sample: mlp 57_26_13
Size: 2.4600 mg
Method: Ramp - Dynamic
Comment: TP1336Na
32.76°C
18.23%
(0.3264mg)
39.69°C
2.739%
(0.0673mg)
70.22°C
78.86°C
147.68°C
4.209%
(0.1035mg)
168.33°C
Temperature (°C)
Universal V3.9A Instruments
100
95
90
85
80
75
0
50
100
150
200
250
300

FIG. 3


Transform Pharmaceuticals, Inc.
Intensity(Counts)
2-Theta(°)
1500
1000
500
0
10
20
40

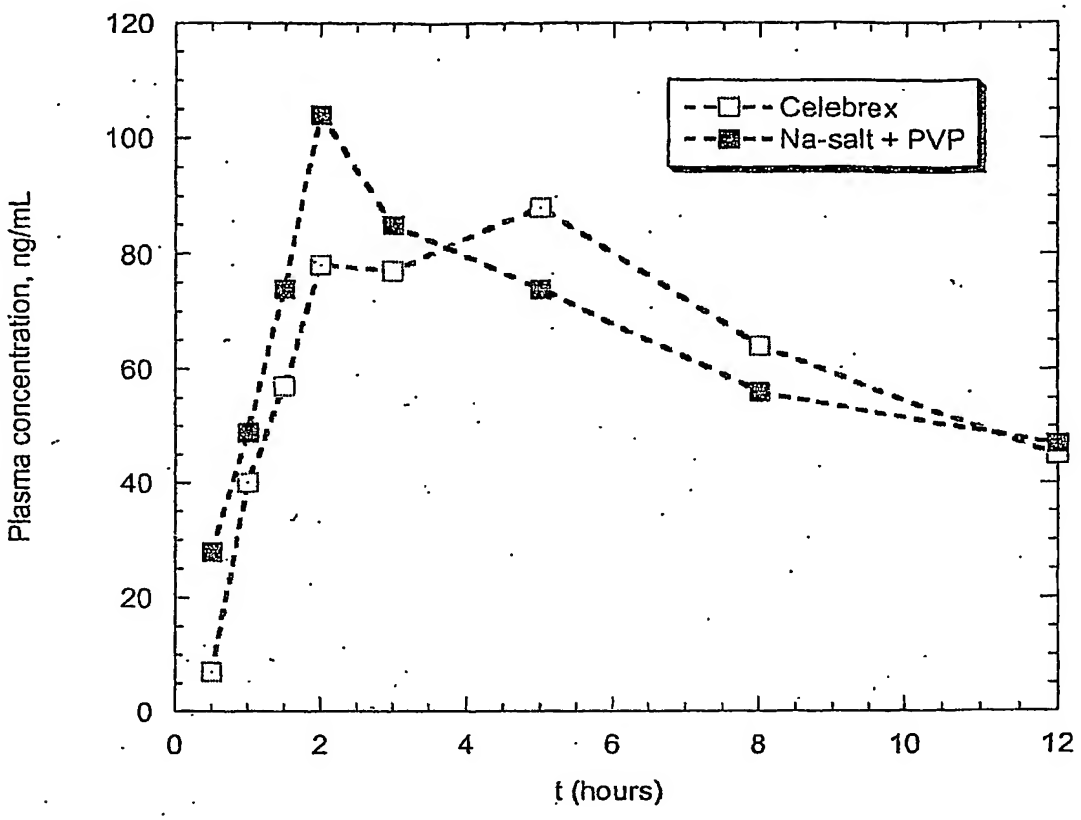

120
100
80
60
40
20
0
Plasma concentration, ng/mL
0
2
4
6
8
10
12
t (hours)
Celebrex
Na-salt + PVP

FIG. 4A

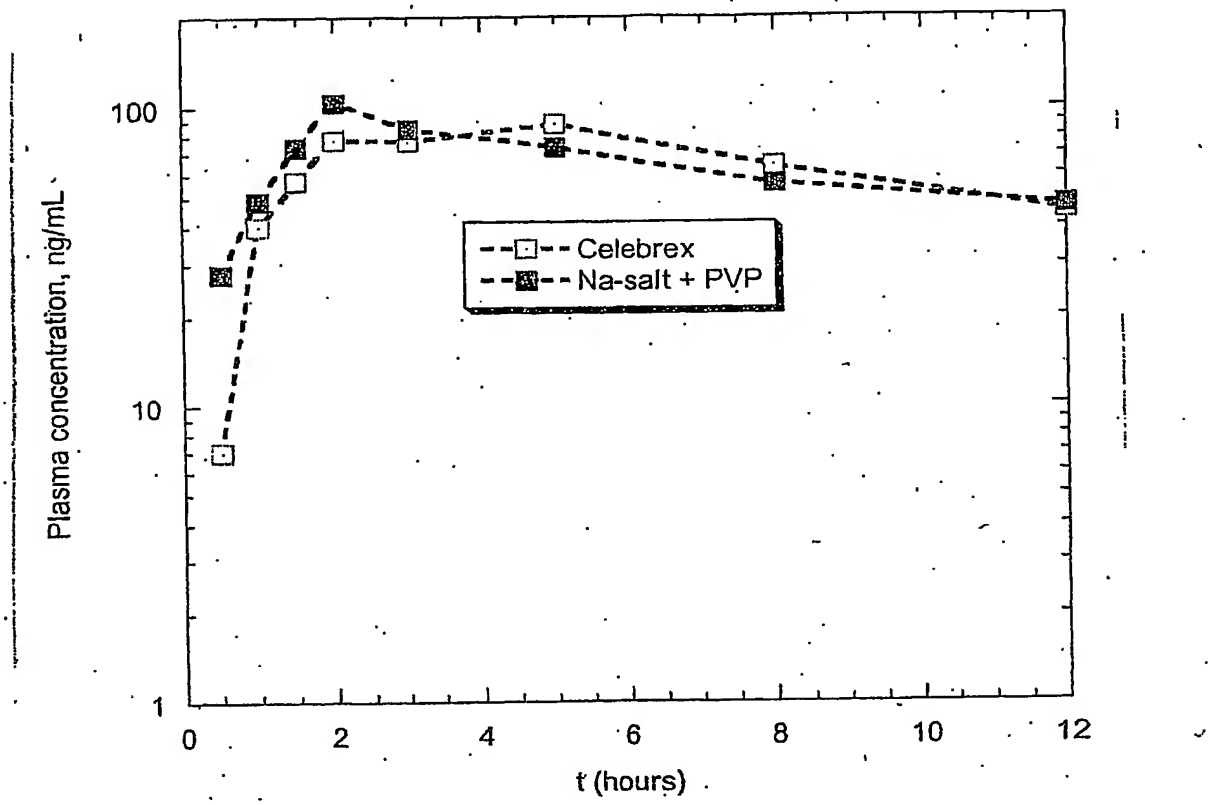

Plasma concentration, ng/mL
100
10
1
0
2
4
6
8
10
12
t (hours)
Celebrex
Na-salt + PVP

FIG. 4B

	Formulation	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (min)	$AUC_{(0-\infty)}$ (ng·hr/mL)	$T_{1/2}$ (hr)	Volume of Distribution at Steady State (mL/kg)	Clearance Rate (mL/hr·kg)	Bioavailability (%)
Mean	Celecoxib IV	1	718	NA	3808	8.21	2498	278	NA
SD		NA	91	NA	933	2.85	590	77	NA
Mean	Celecoxib PO	5.09	654	1.25	7663	9.3	NA	798	40.05
SD		0.050	199	0.88	3119	3.48	NA	317	15.45
Mean	Celecoxib Sodium PO	5.05	2142	0.75	16426	9.0	NA	323	85.80
SD		0.121	569	0.27	4150	2.71	NA	77	7.82

FIG. 5

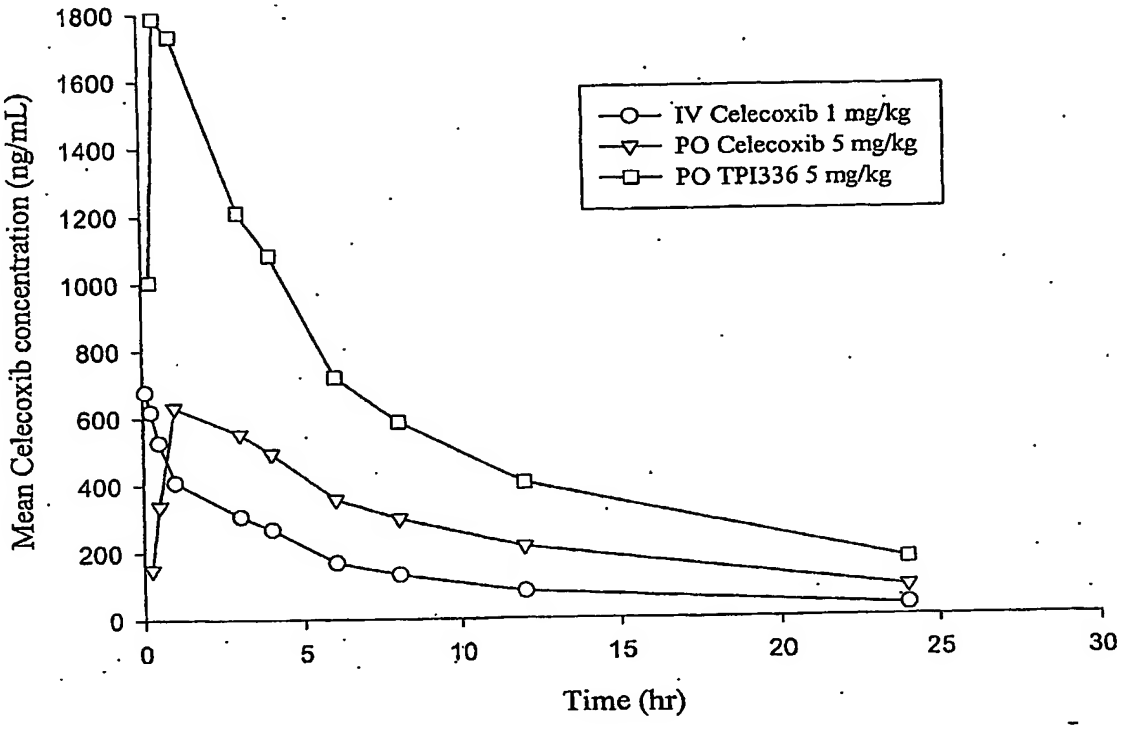
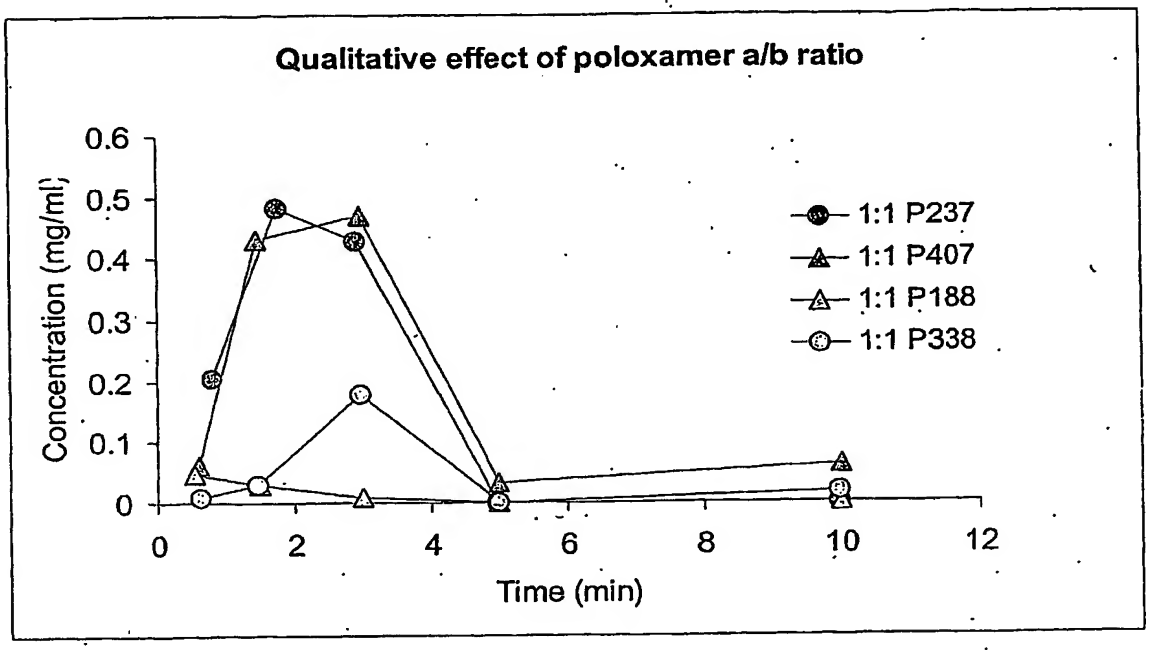

Mean Celecoxib concentration (ng/mL)
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
Time (hr)
IV Celecoxib 1 mg/kg
PO Celecoxib 5 mg/kg
PO TPI336 5 mg/kg

FIG. 6

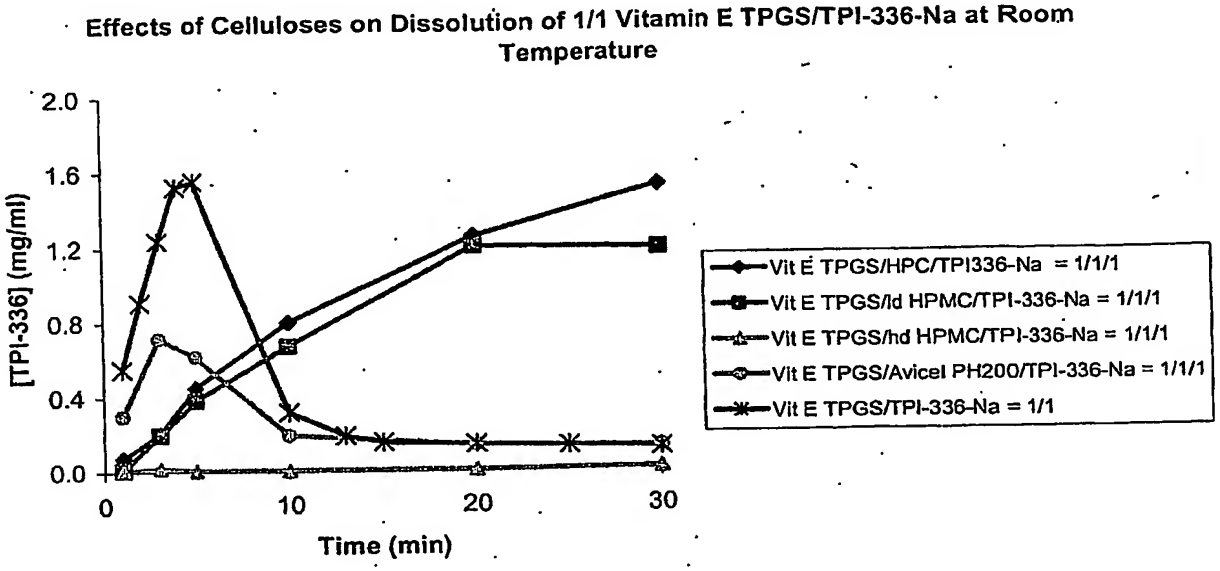


Poloxamer	Physical form	a	b	Average molecular weight
124	Liquid	12	20	2090-2360
188	Solid	80	27	7680-9510
P237	Solid	64	37	6840-8830
338	Solid	141	44	12 700-17 400
P407	Solid	101	56	9840-14 600

Percent a	Percent b	Ratio a/b
0.38	0.63	0.60
0.75	0.25	2.96
0.63	0.37	1.73
0.76	0.24	3.20
0.64	0.36	1.80

$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$

FIG. 7



hd HPMC = High density
ld HPMC = low density

FIG. 8

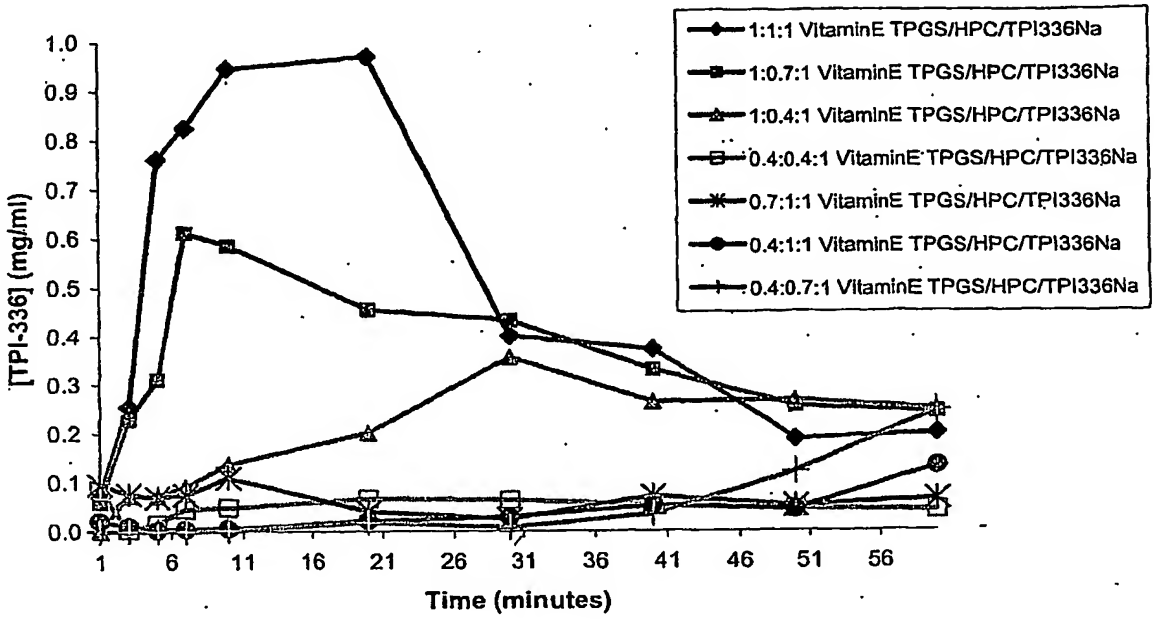

1:1:1 VitaminE TPGS/HPC/TPI336Na
1:0.7:1 VitaminE TPGS/HPC/TPI336Na
1:0.4:1 VitaminE TPGS/HPC/TPI336Na
0.4:0.4:1 VitaminE TPGS/HPC/TPI336Na
0.7:1:1 VitaminE TPGS/HPC/TPI336Na
0.4:1:1 VitaminE TPGS/HPC/TPI336Na
0.4:0.7:1 VitaminE TPGS/HPC/TPI336Na
[TPI-336] (mg/ml)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1
6
11
16
21
26
31
36
41
46
51
56
Time (minutes)

FIG. 9

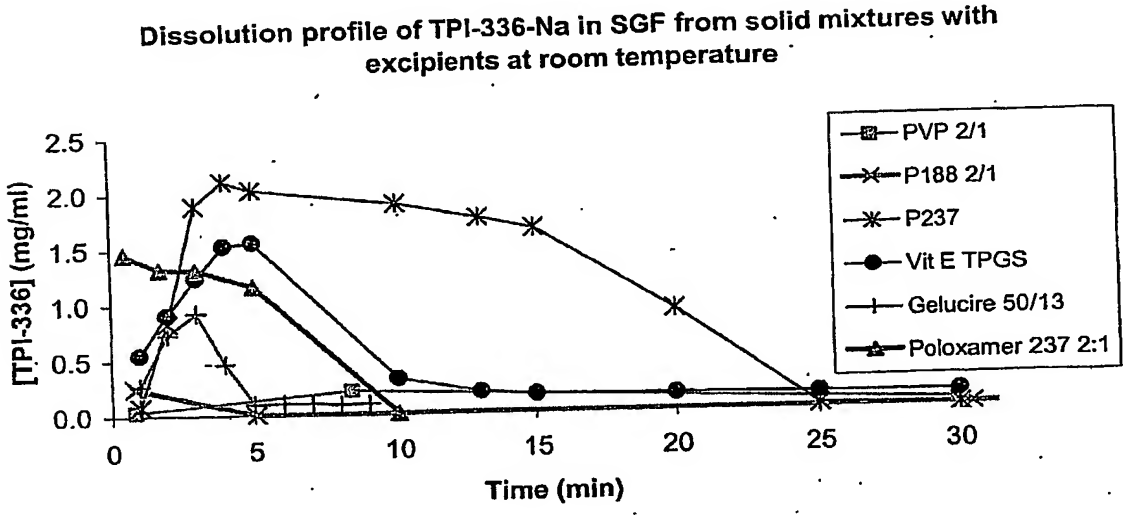

Dissolution profile of TPI-336-Na in SGF from solid mixtures with excipients at room temperature
[TPI-336] (mg/ml)
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
Time (min)
PVP 2/1
P188 2/1
P237
Vit E TPGS
Gelucire 50/13
Poloxamer 237 2:1

FIG. 10

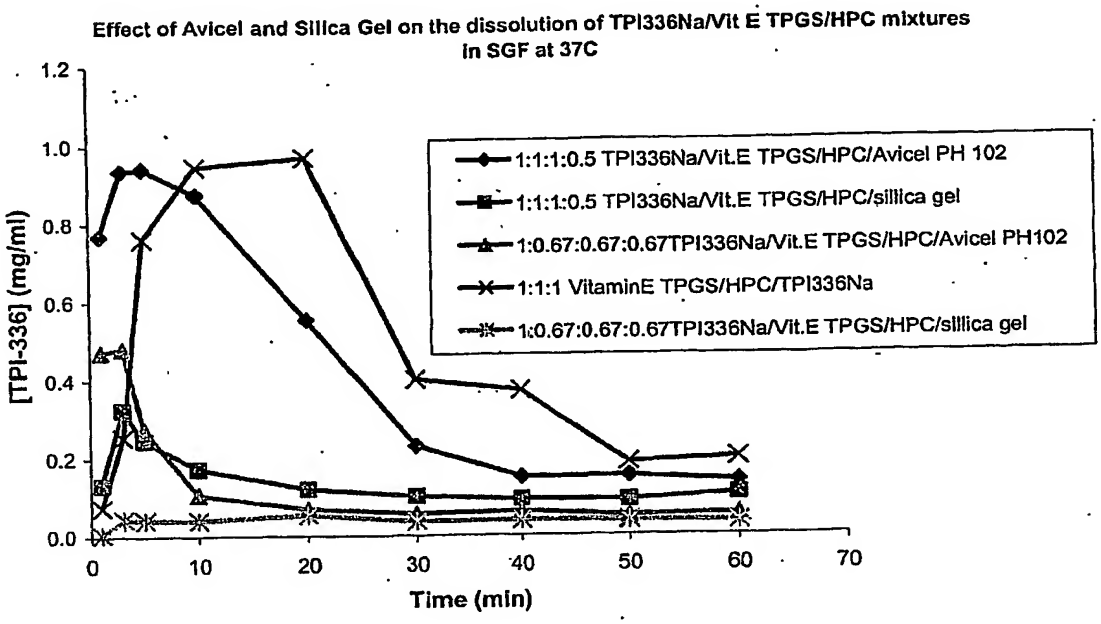

Effect of Avicel and Silica Gel on the dissolution of TPI336Na/Vit E TPGS/HPC mixtures in SGF at 37C
[TPI-336] (mg/ml)
Time (min)
1:1:1:0.5 TPI336Na/Vit.E TPGS/HPC/Avicel PH 102
1:1:1:0.5 TPI336Na/Vit.E TPGS/HPC/silica gel
1:0.67:0.67:0.67TPI336Na/Vit.E TPGS/HPC/Avicel PH102
1:1:1 VitaminE TPGS/HPC/TPI336Na
1:0.67:0.67:0.67TPI336Na/Vit.E TPGS/HPC/silica gel

FIG. 11

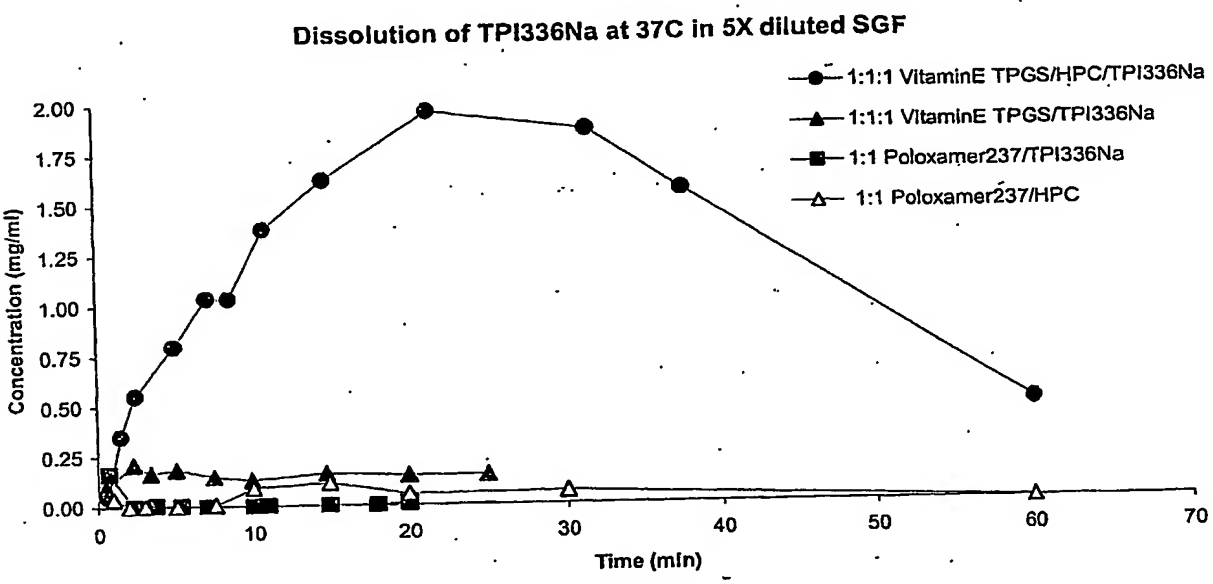

Dissolution of TPI336Na at 37C in 5X diluted SGF
1:1:1 VitaminE TPGS/HPC/TPI336Na
1:1:1 VitaminE TPGS/TPI336Na
1:1 Poloxamer237/TPI336Na
1:1 Poloxamer237/HPC
Concentration (mg/ml)
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
Time (min)

FIG. 12

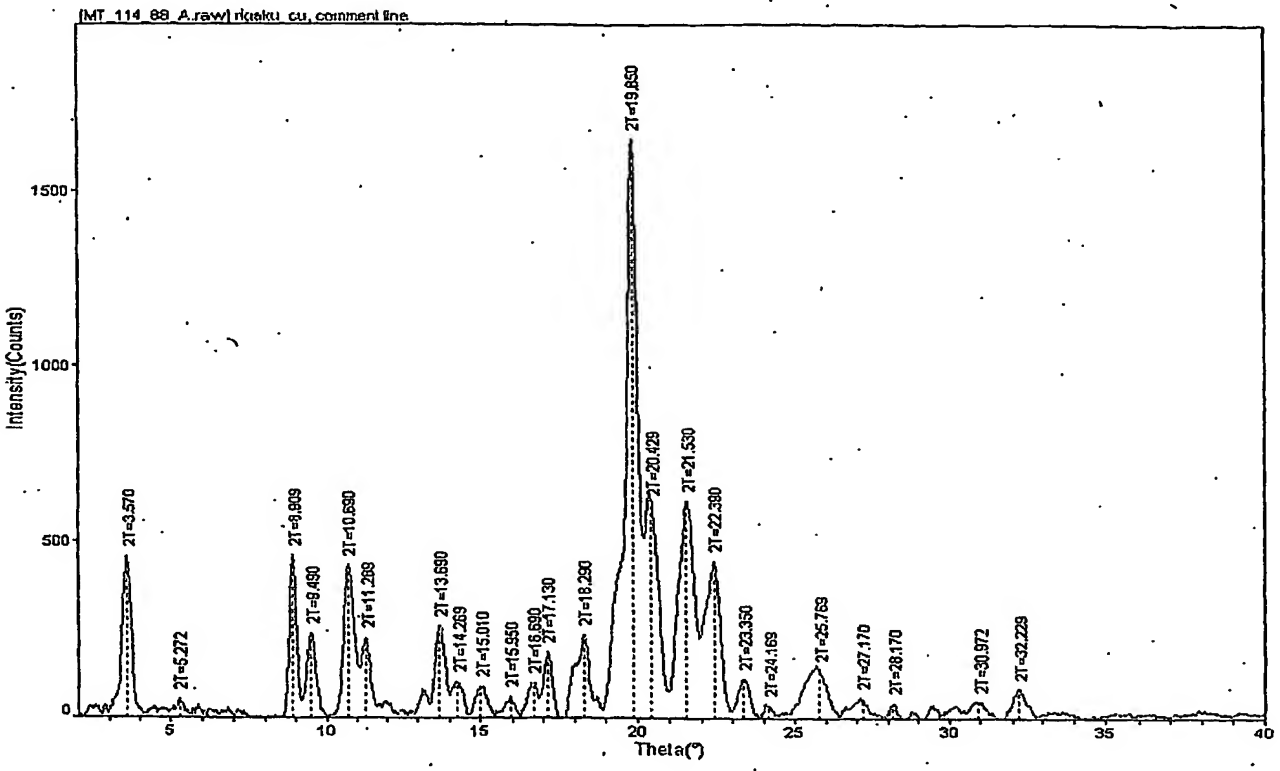

[MT_114_88_A.raw] rigaku_cu, comment line
Intensity(Counts)
Theta(°)
2T=3.570
2T=5.272
2T=8.909
2T=9.490
2T=10.690
2T=11.269
2T=13.690
2T=14.269
2T=15.010
2T=15.550
2T=16.690
2T=17.130
2T=18.290
2T=19.850
2T=20.429
2T=21.530
2T=22.390
2T=23.350
2T=24.169
2T=25.769
2T=27.170
2T=28.170
2T=30.972
2T=32.229

FIG. 13A

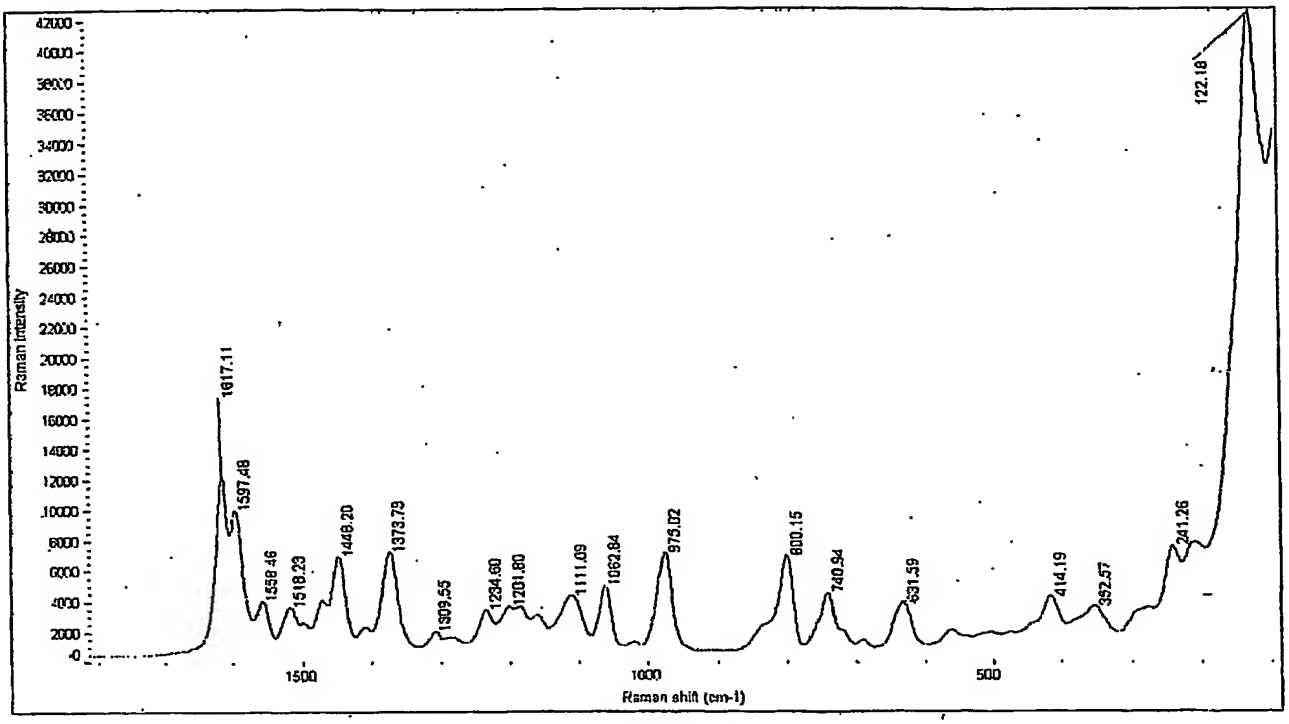

Raman Intensity
Raman shift (cm-1)
1617.11
1597.48
1538.46
1518.23
1448.20
1373.73
1309.55
1234.60
1201.60
1111.09
1062.84
975.02
800.15
740.94
631.59
414.19
362.57
241.26
122.18

FIG. 13B

FIG. 14

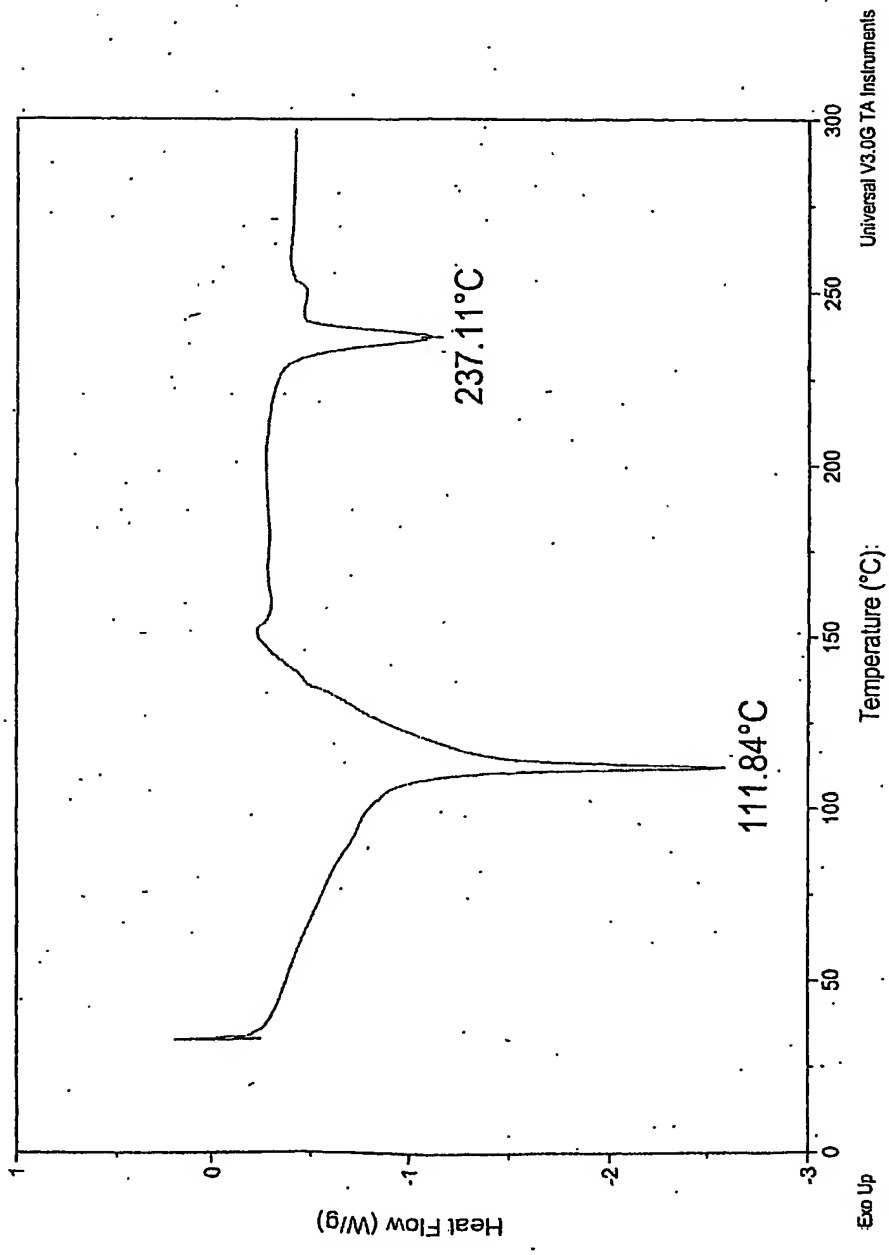

237.11°C
111.84°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V3.0G TA Instruments

FIG. 15

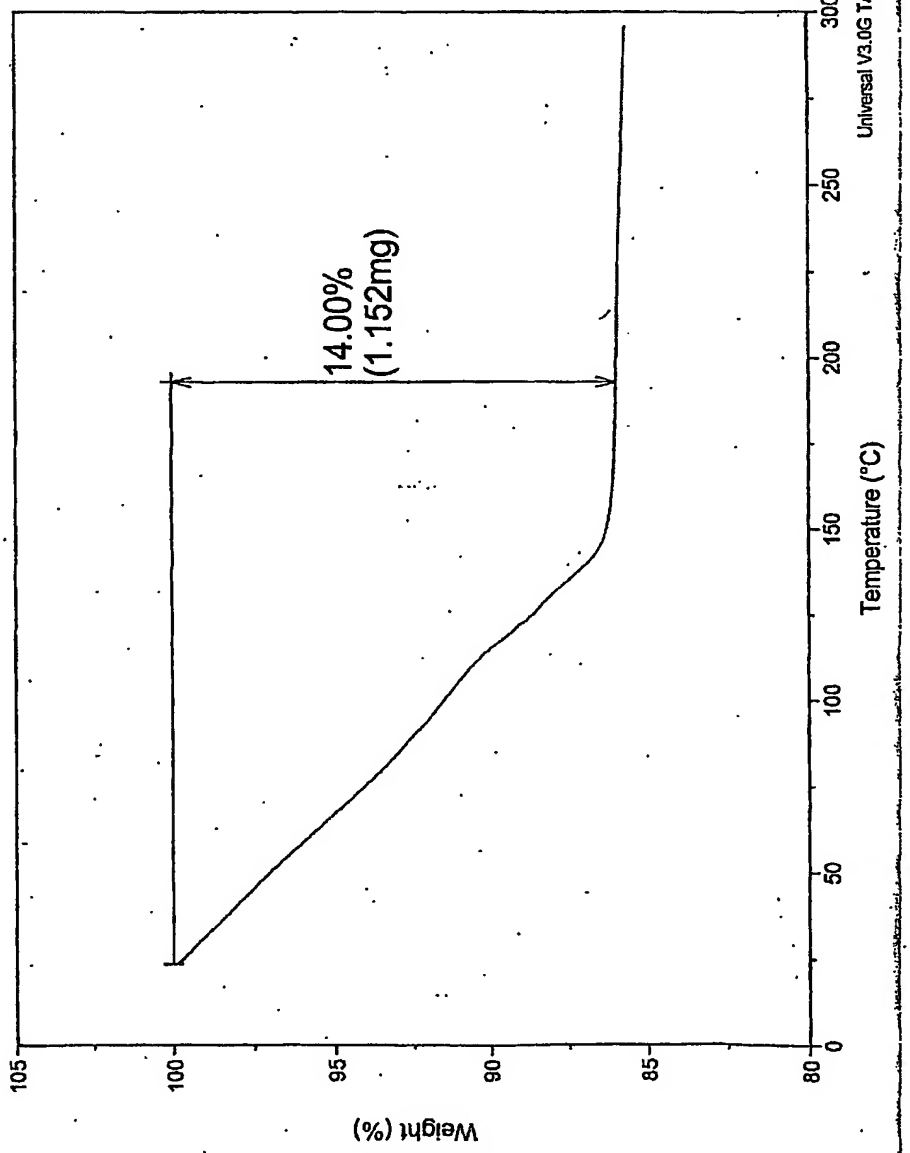

14.00%
(1.152mg)
Universal V3.0G TA Instruments
Temperature (°C)
Weight (%)
105
100
95
90
85
80
0
50
100
150
200
250
300

FIG. 16

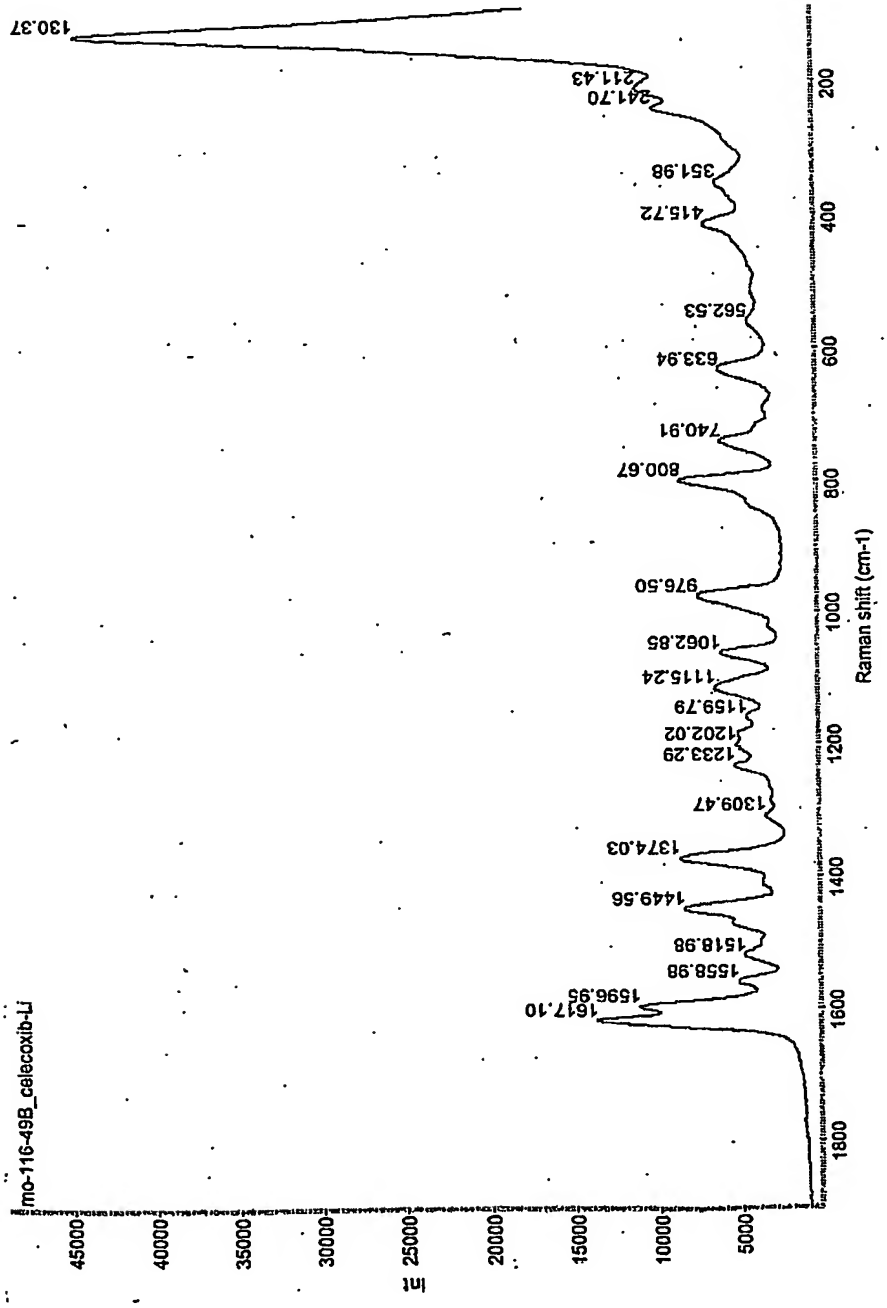

mo-116-49B_celecoxib-LI
Raman shift (cm-1)
Int
130.37
211.43
241.70
351.98
415.72
562.53
633.94
740.91
800.67
976.50
1062.85
1115.24
1159.79
1202.02
1233.29
1309.47
1374.03
1449.56
1518.98
1558.98
1596.95
1617.10

FIG. 17

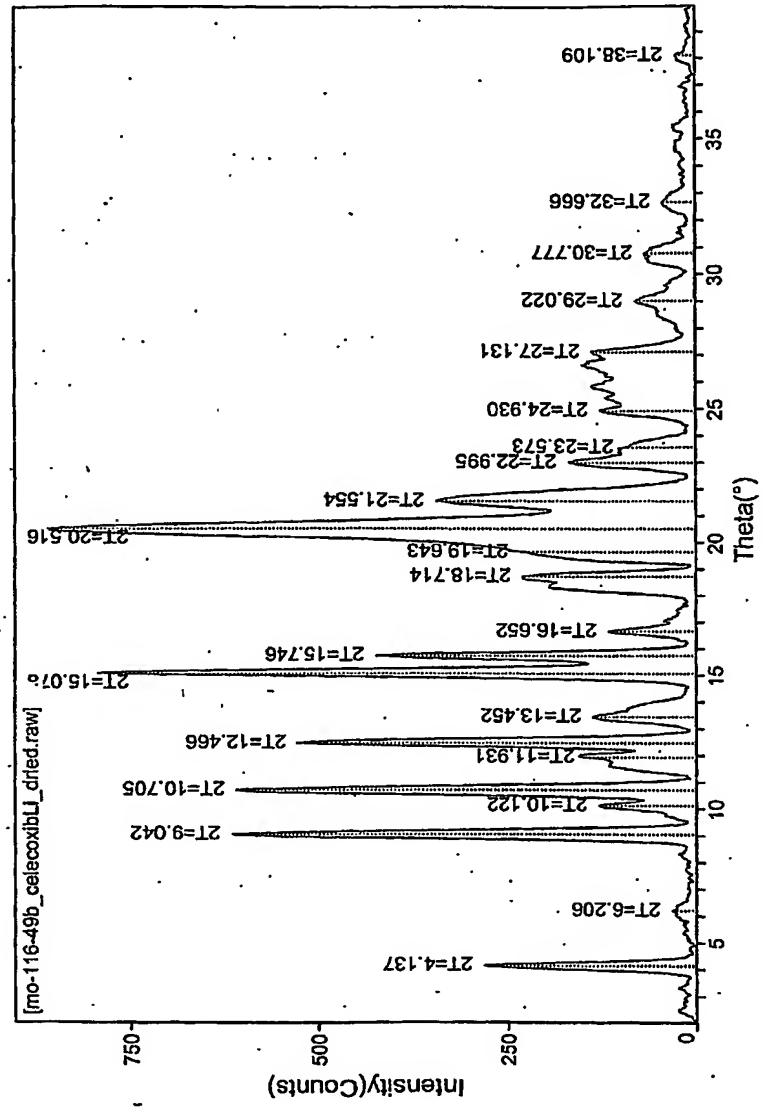

2T=38.109
2T=32.666
2T=30.777
2T=29.022
2T=27.131
2T=24.930
2T=23.573
2T=22.995
2T=21.554
2T=20.516
2T=19.643
2T=18.714
2T=16.652
2T=15.746
2T=15.076
2T=13.452
2T=12.466
2T=11.931
2T=10.705
2T=10.122
2T=9.042
2T=6.206
2T=4.137
[mo-116-49b_celecoxibLI_dried.raw]
Intensity(Counts)
750
500
250
0
5
10
15
20
25
30
35
Theta(°)

FIG. 18

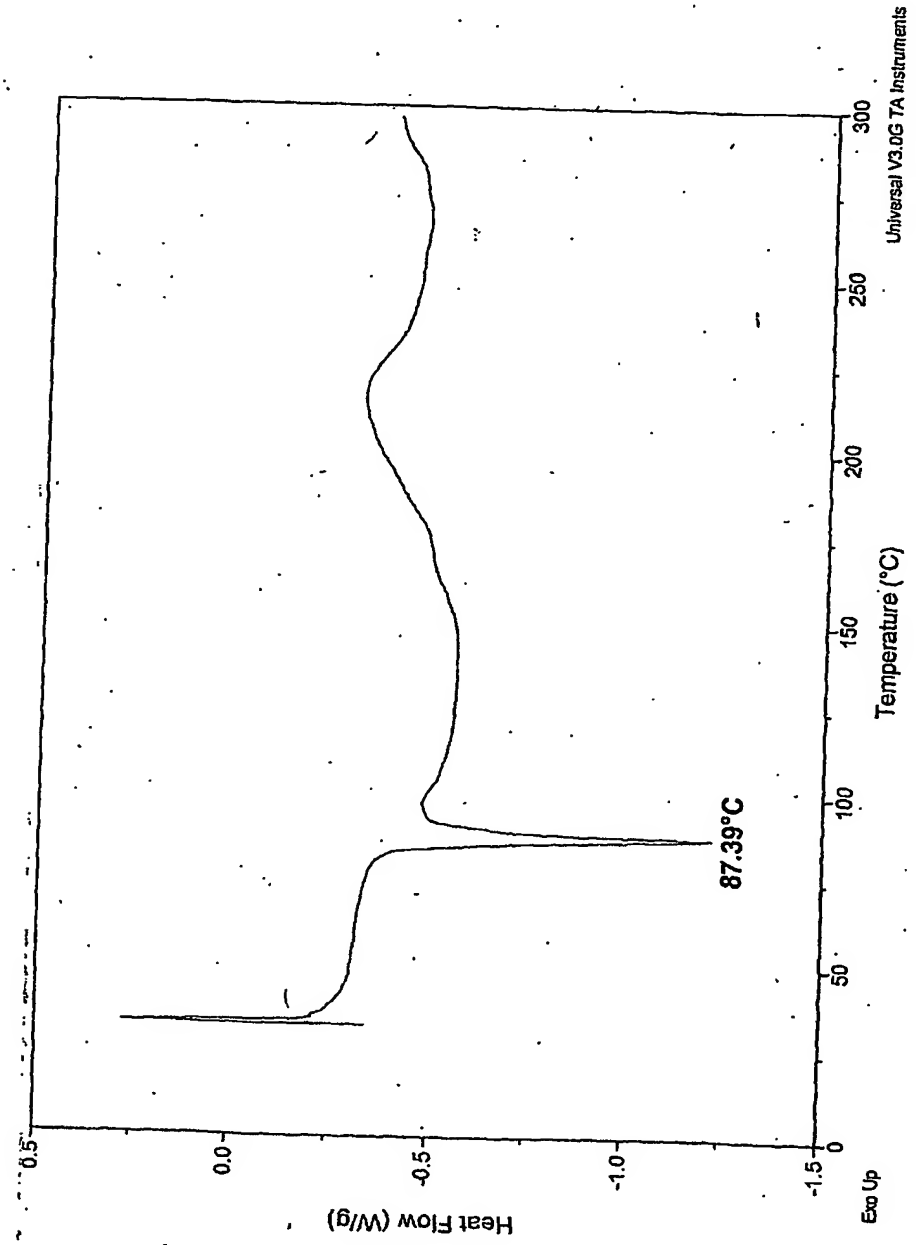

Universal V3.0G TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Up
87.39°C
0.5
0.0
-0.5
-1.0
-1.5
0
50
100
150
200
250
300

FIG. 19

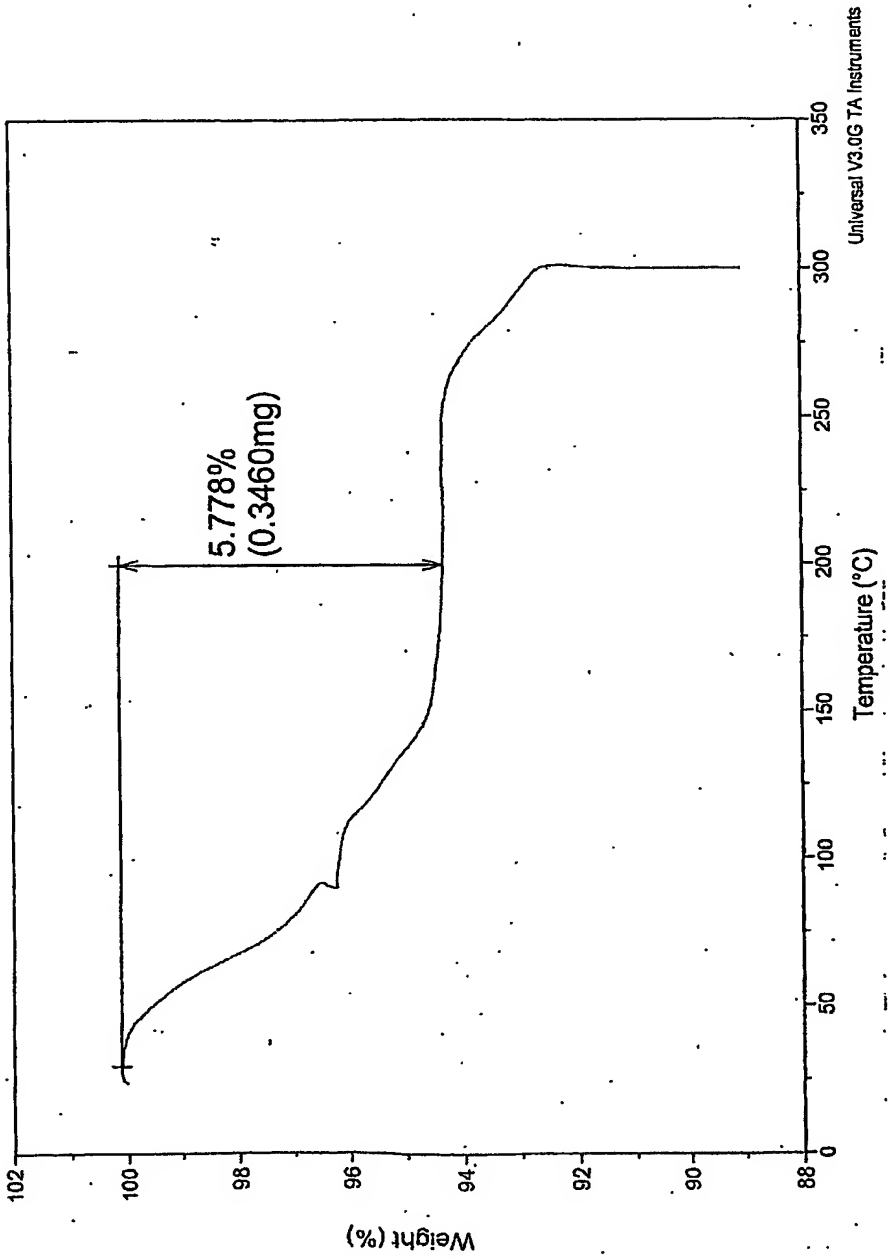

5.778%
(0.3460mg)
Weight (%)
Temperature (°C)
Universal V3.0G TA Instruments

FIG. 20

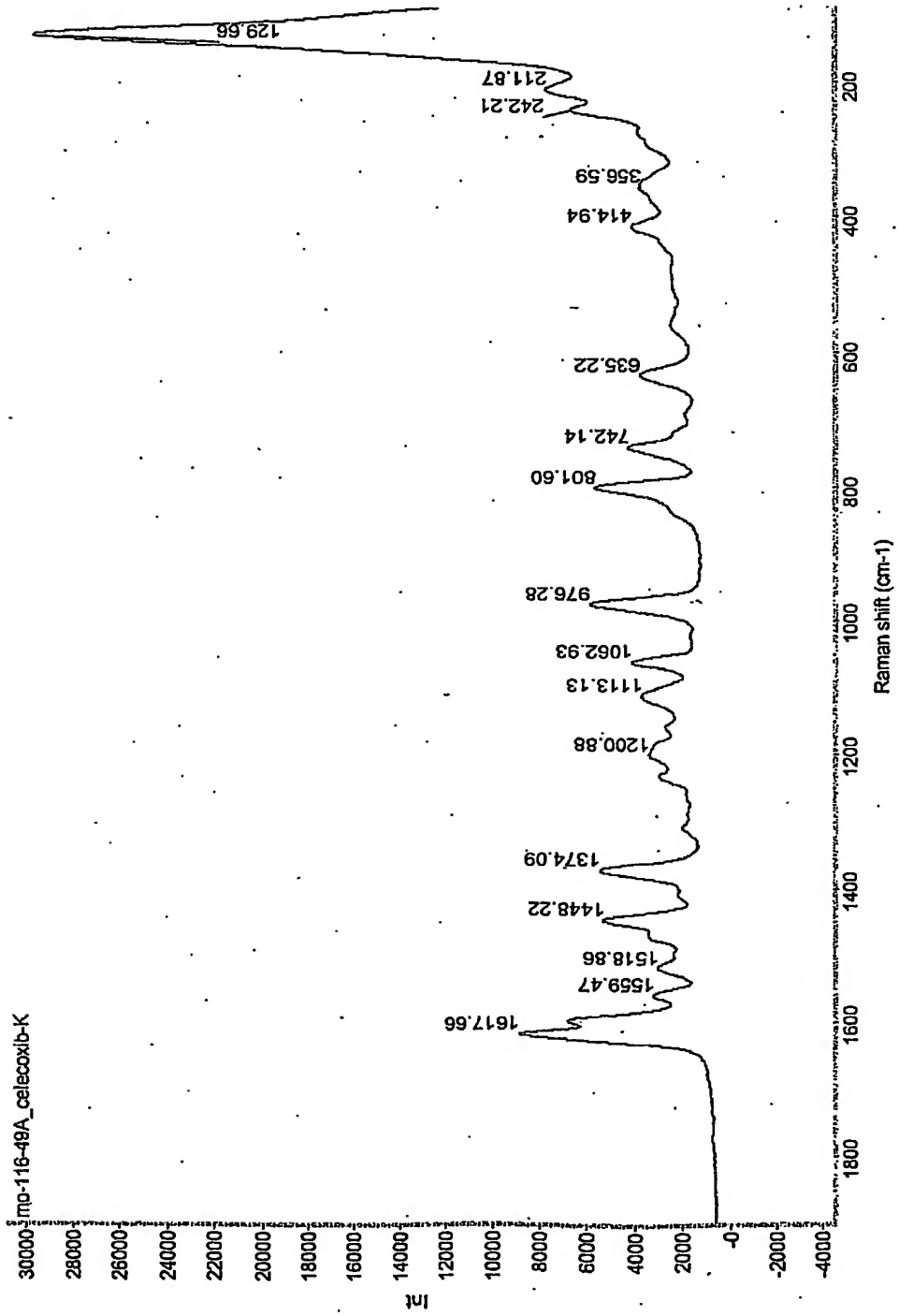

mp-116-49A_celecoxib-K
Int
Raman shift (cm-1)
129.66
211.87
242.21
356.59
414.94
635.22
742.14
801.60
976.28
1062.93
1113.13
1200.88
1374.09
1448.22
1518.86
1559.47
1617.66

FIG. 21

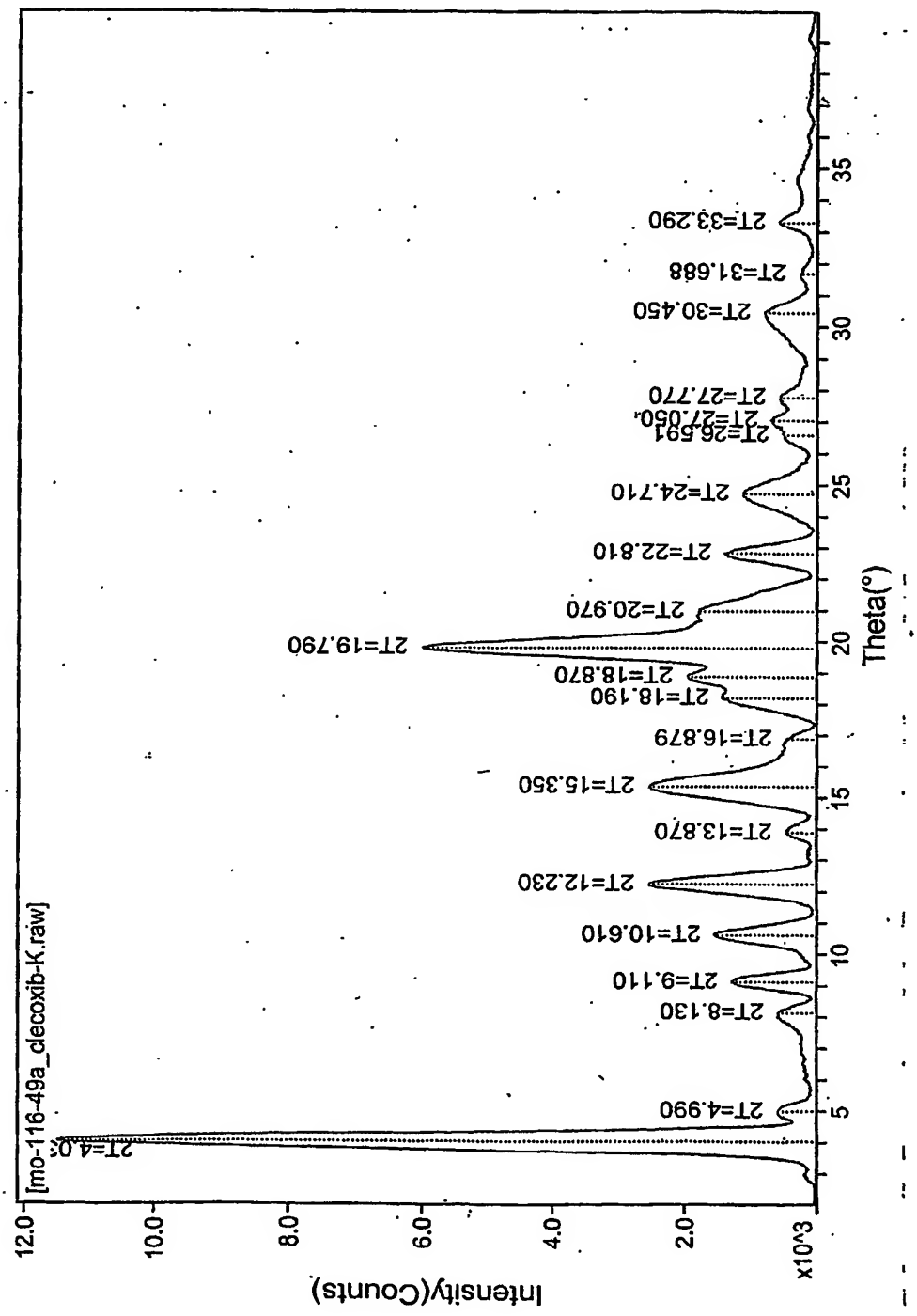

[mo-116-49a_clecoxib-K.raw]
2T=4.0
2T=4.990
2T=8.130
2T=9.110
2T=10.610
2T=12.230
2T=13.870
2T=15.350
2T=16.879
2T=18.190
2T=18.870
2T=19.790
2T=20.970
2T=22.810
2T=24.710
2T=26.591
2T=27.050
2T=27.770
2T=30.450
2T=31.688
2T=33.290
Theta(°)
Intensity(Counts)
x10^3

FIG. 22

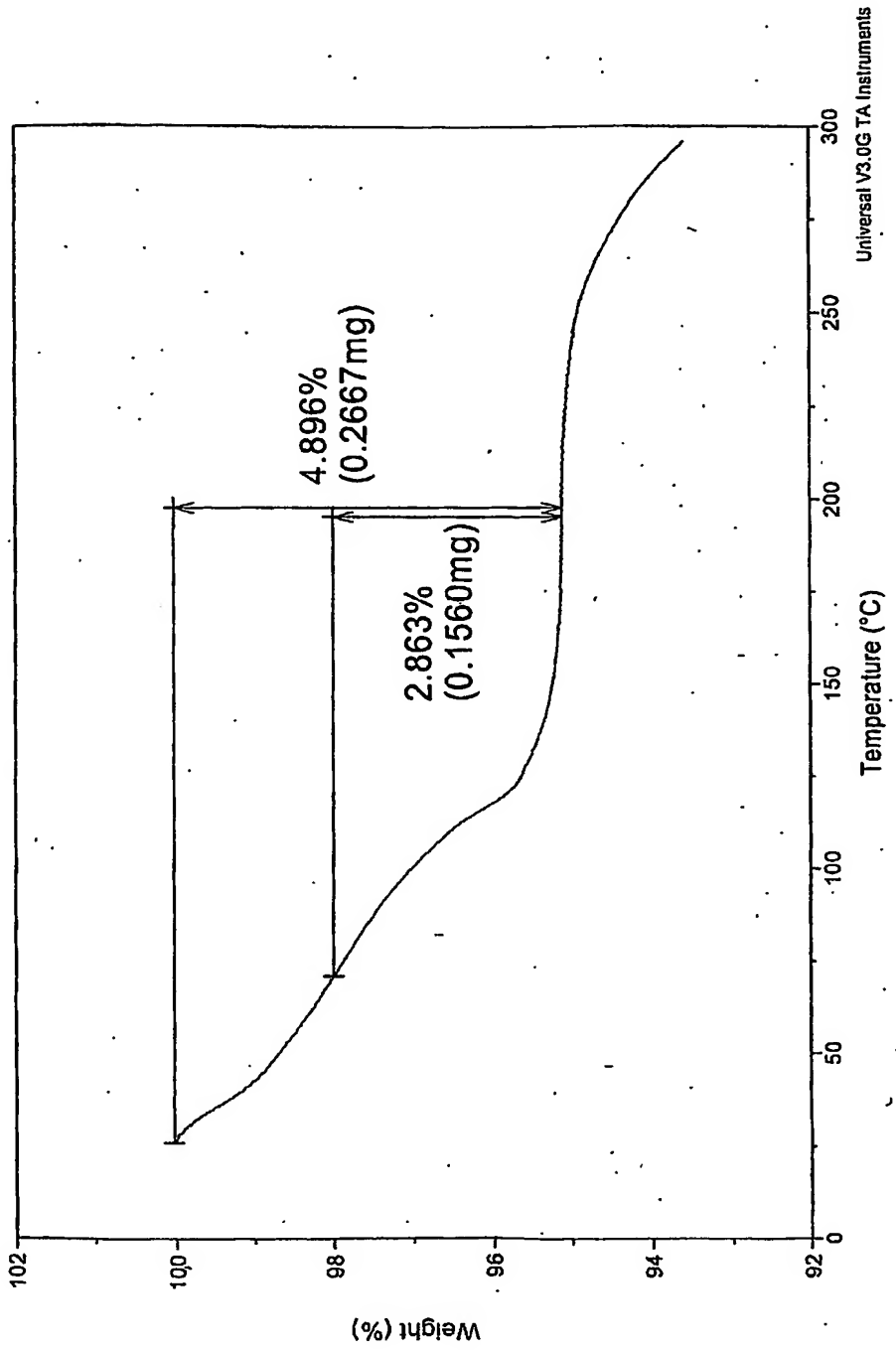

Universal V3.0G TA Instruments
4.896%
(0.2667mg)
2.863%
(0.1560mg)
Temperature (°C)
Weight (%)
0
50
100
150
200
250
300
92
94
96
98
100
102

FIG. 23

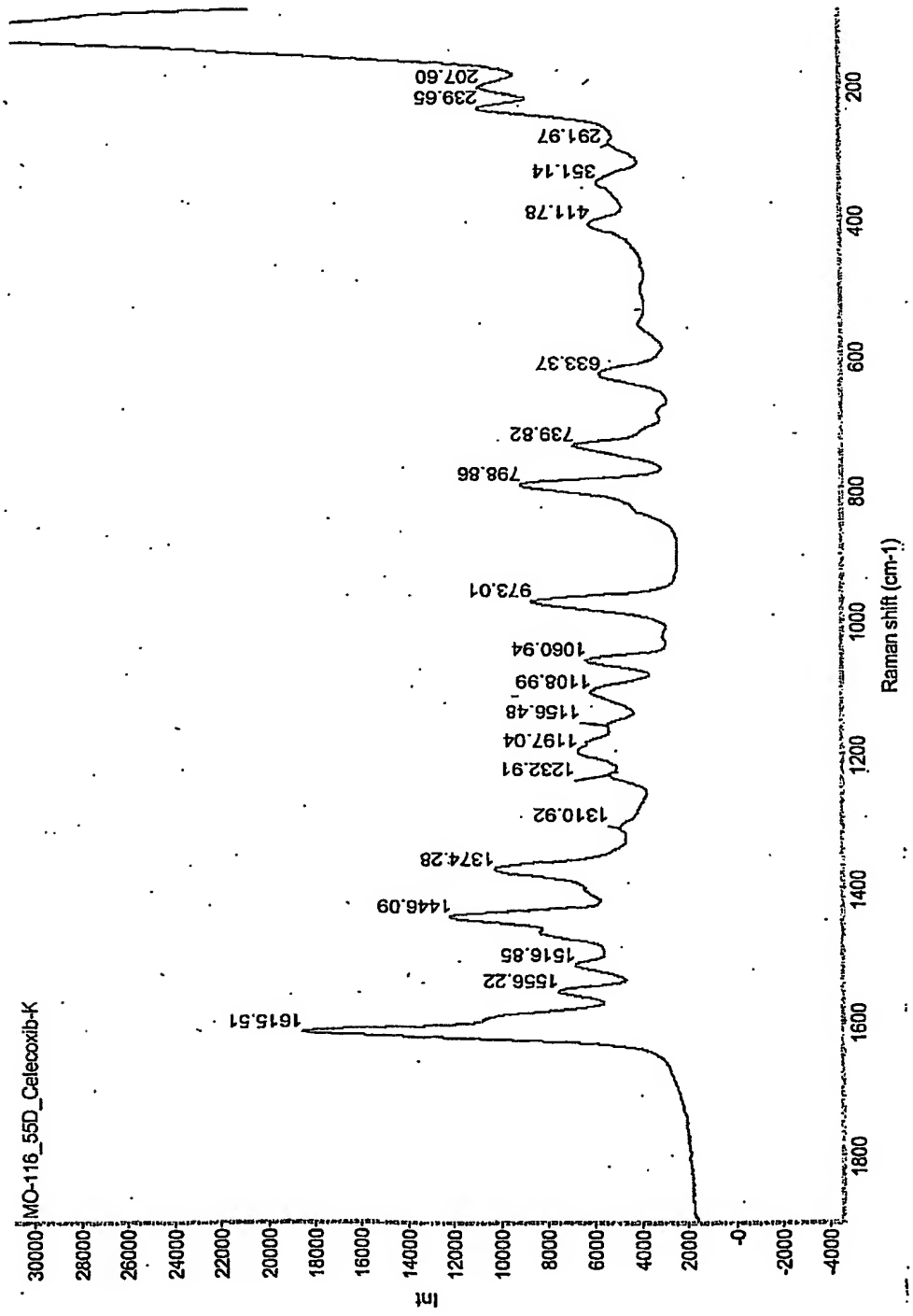

MO-116_55D_Celecoxib-K
Int
Raman shift (cm-1)
1615.51
1556.22
1516.85
1446.09
1374.28
1310.92
1232.91
1197.04
1156.48
1108.99
1060.94
973.01
798.86
739.82
633.37
411.78
351.14
291.97
239.65
207.60

FIG. 24

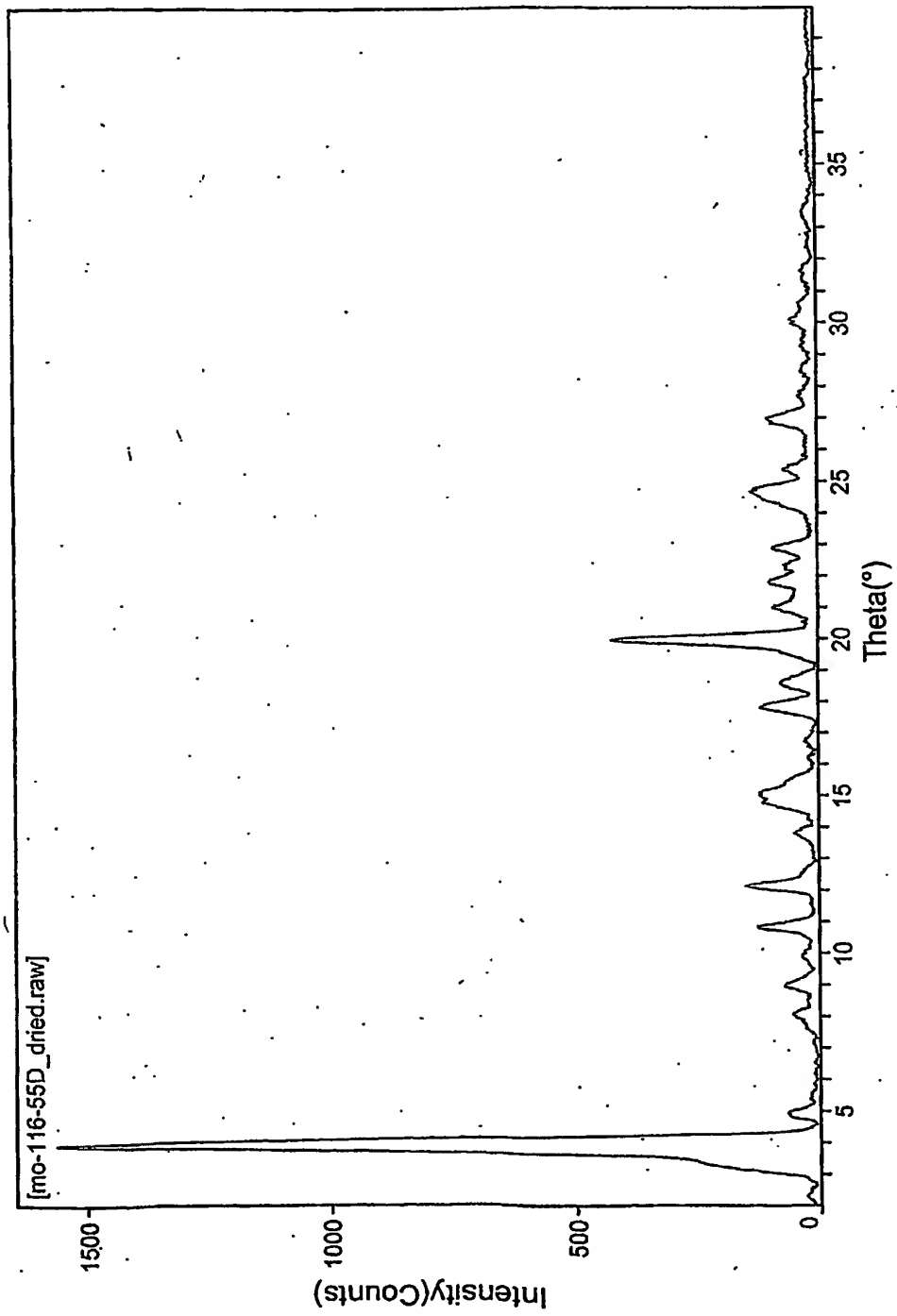

[mo-116-55D_dried.raw]
Intensity(Counts)
1500
1000
500
0
5
10
15
20
25
30
35
Theta(°)

FIG. 25

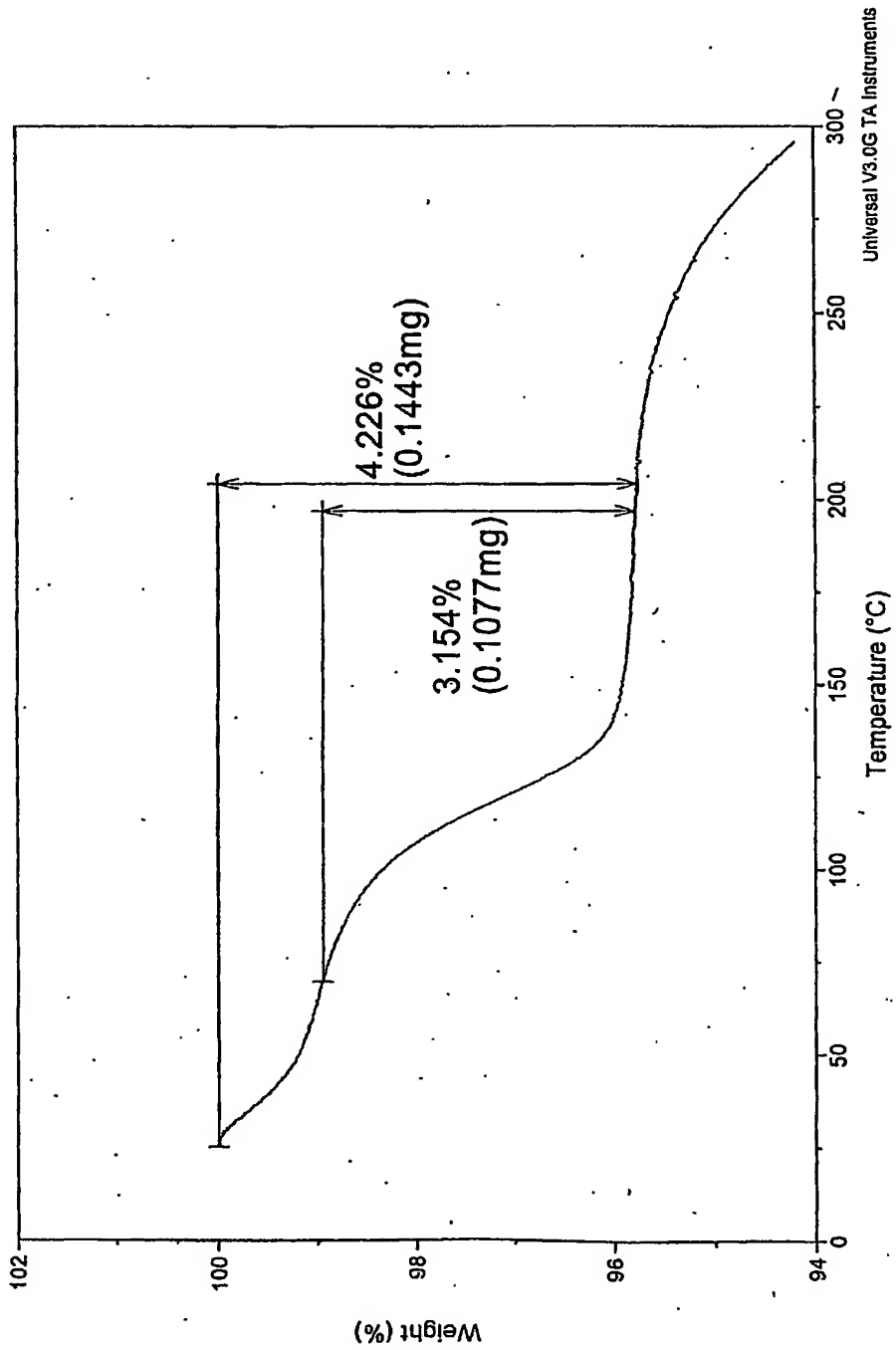

Universal V3.0G TA Instruments
4.226%
(0.1443mg)
3.154%
(0.1077mg)
Temperature (°C)
Weight (%)
102
100
98
96
94
0
50
100
150
200
250
300

FIG. 26

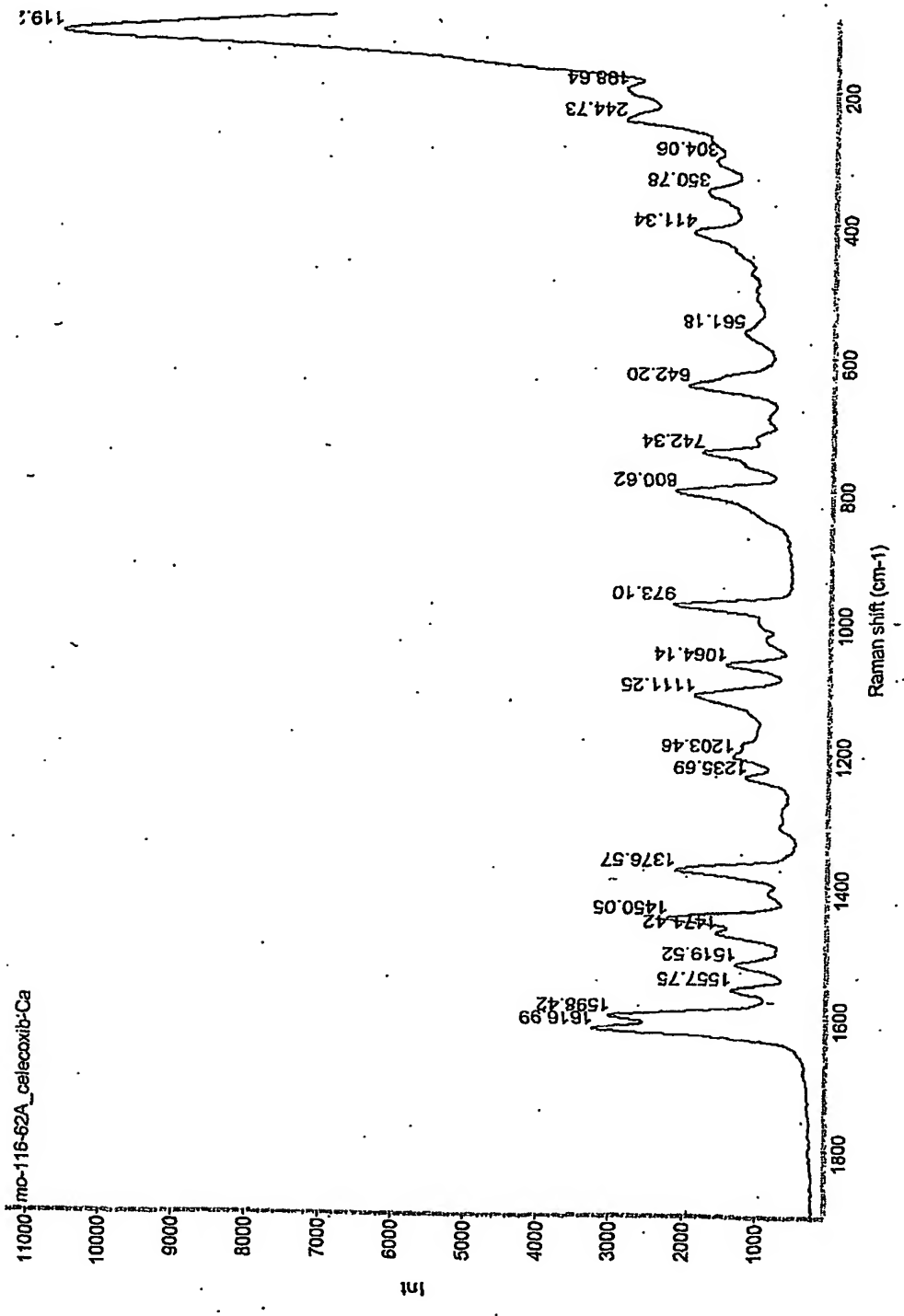

mo-116-62A_celecoxib-Ca
Int
Raman shift (cm-1)
119.5
188.64
244.73
304.06
350.78
411.34
561.18
642.20
742.34
800.62
973.10
1064.14
1111.25
1203.46
1235.69
1376.57
1450.05
1474.42
1519.52
1557.75
1598.42
1616.99

FIG. 27

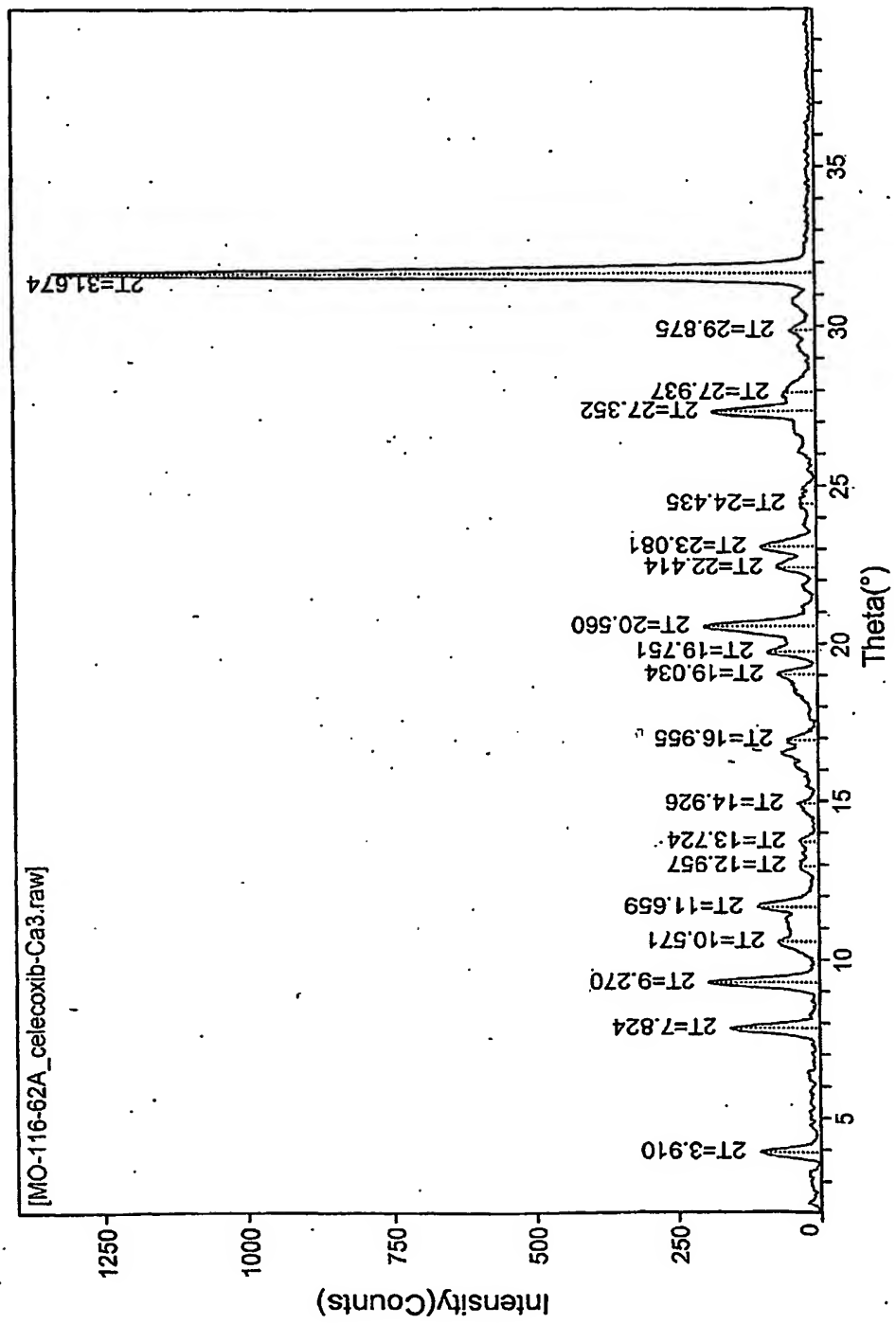

[MO-116-62A_celecoxib-Ca3.raw]
2T=3.910
2T=7.824
2T=9.270
2T=10.571
2T=11.659
2T=12.957
2T=13.724
2T=14.926
2T=16.955
2T=19.034
2T=19.751
2T=20.560
2T=22.414
2T=23.081
2T=24.435
2T=27.352
2T=27.937
2T=29.875
2T=31.674
Intensity(Counts)
Theta(°)

FIG. 28

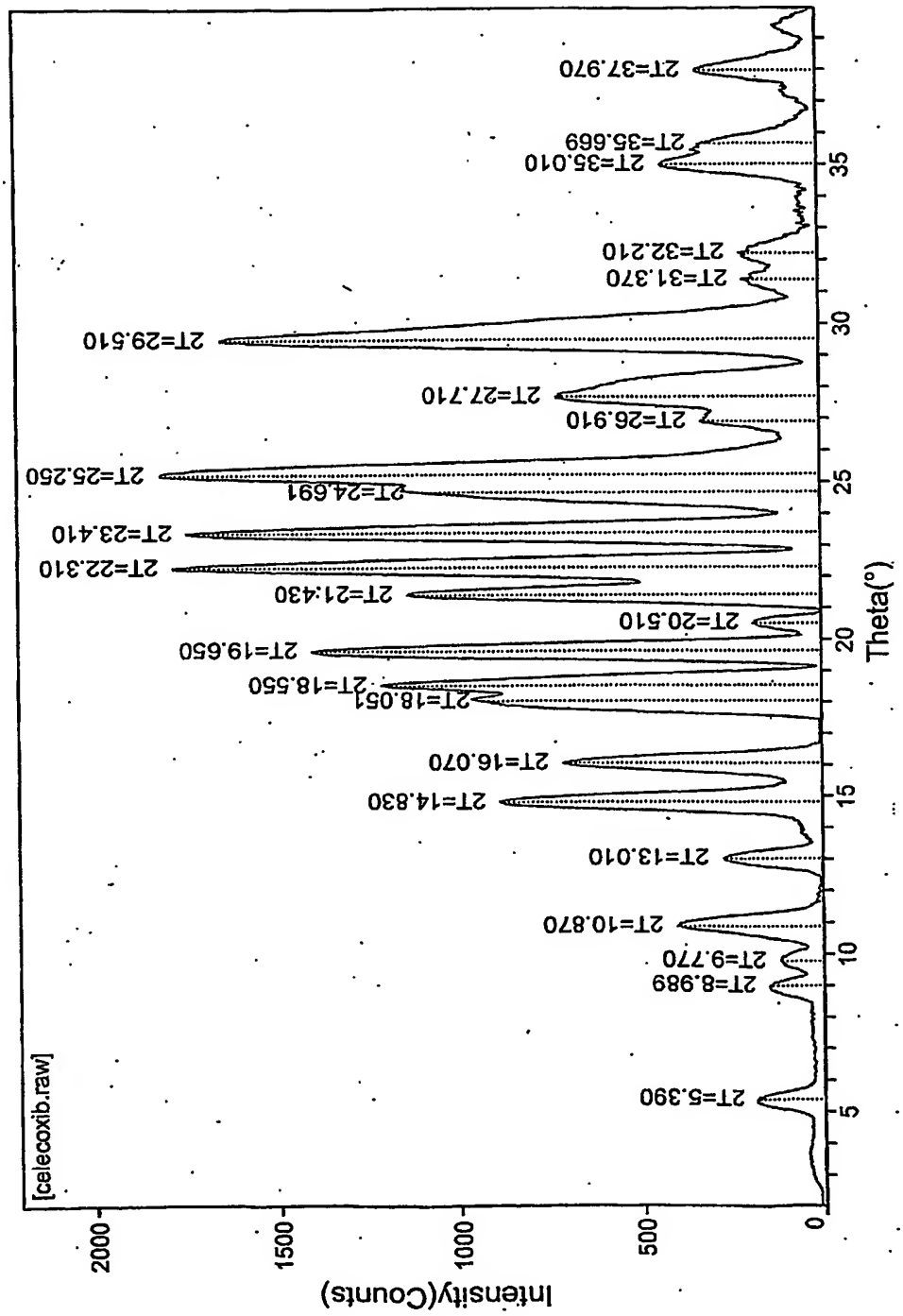

[celecoxib.raw]
Intensity(Counts)
Theta(°)
2T=5.390
2T=8.989
2T=9.770
2T=10.870
2T=13.010
2T=14.830
2T=16.070
2T=18.051
2T=18.550
2T=19.650
2T=20.510
2T=21.430
2T=22.310
2T=23.410
2T=24.691
2T=25.250
2T=26.910
2T=27.710
2T=29.510
2T=31.370
2T=32.210
2T=35.010
2T=35.669
2T=37.970

FIG. 29

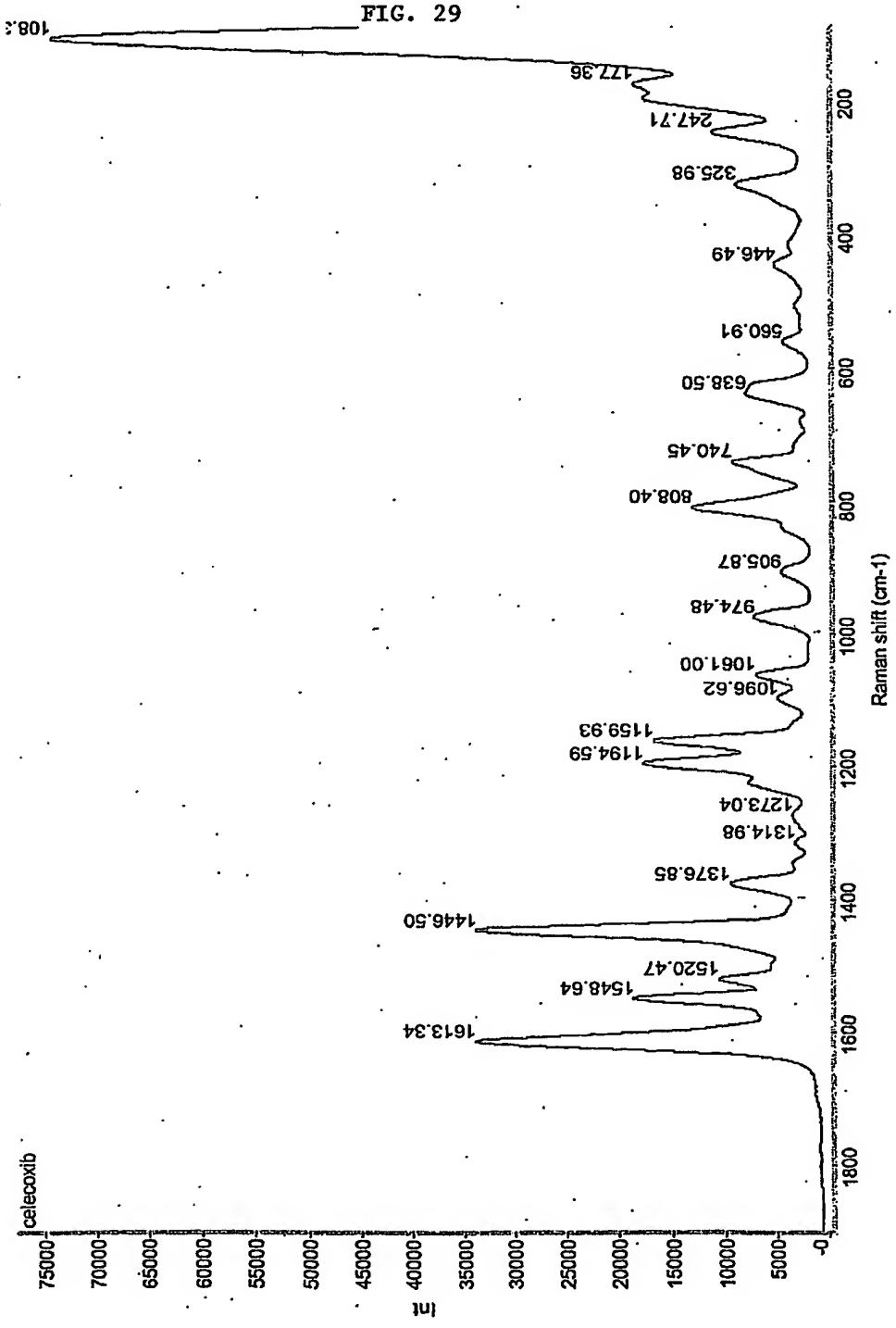

celecoxib
Int
Raman shift (cm-1)
108.3
177.36
247.71
325.98
446.49
560.91
638.50
740.45
808.40
905.87
974.48
1061.00
1096.62
1159.93
1194.59
1273.04
1314.98
1376.85
1446.50
1520.47
1548.64
1613.34

FIG. 30

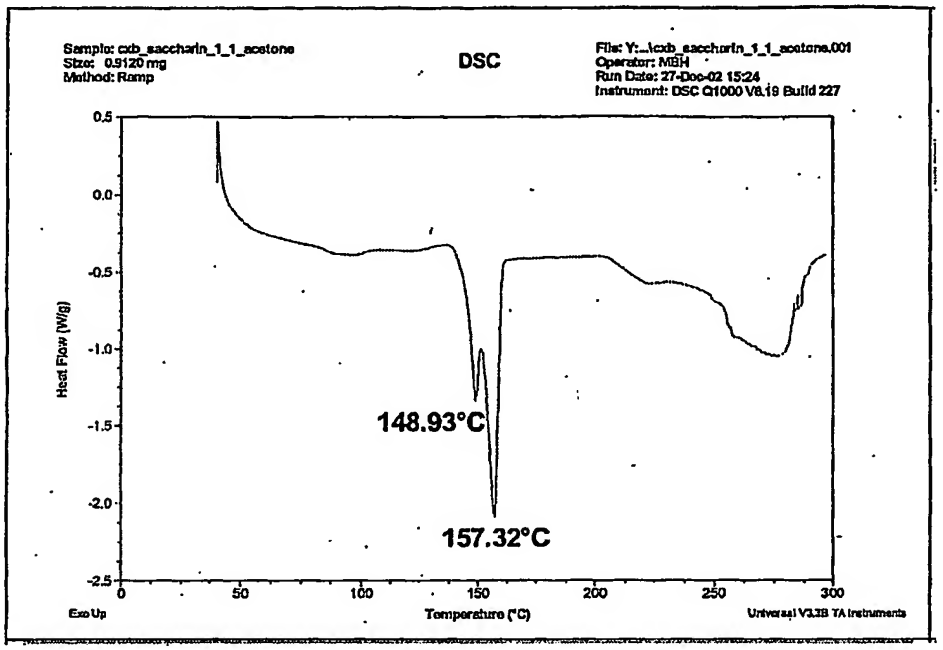

Sample: cxb_saccharin_1_1_acetone
Size: 0.9120 mg
Method: Ramp
DSC
File: Y:...\cxb_saccharin_1_1_acetone.001
Operator: MBH
Run Date: 27-Dec-02 15:24
Instrument: DSC Q1000 V8.19 Build 227
Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
148.93°C
157.32°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)
Universal V3.3B TA Instruments

FIG. 31

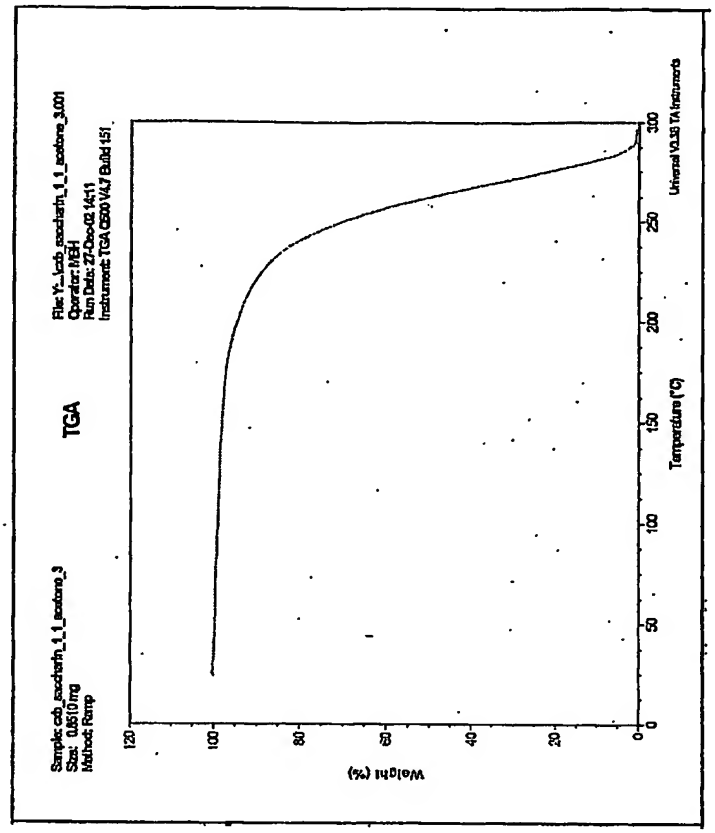


FIG. 32

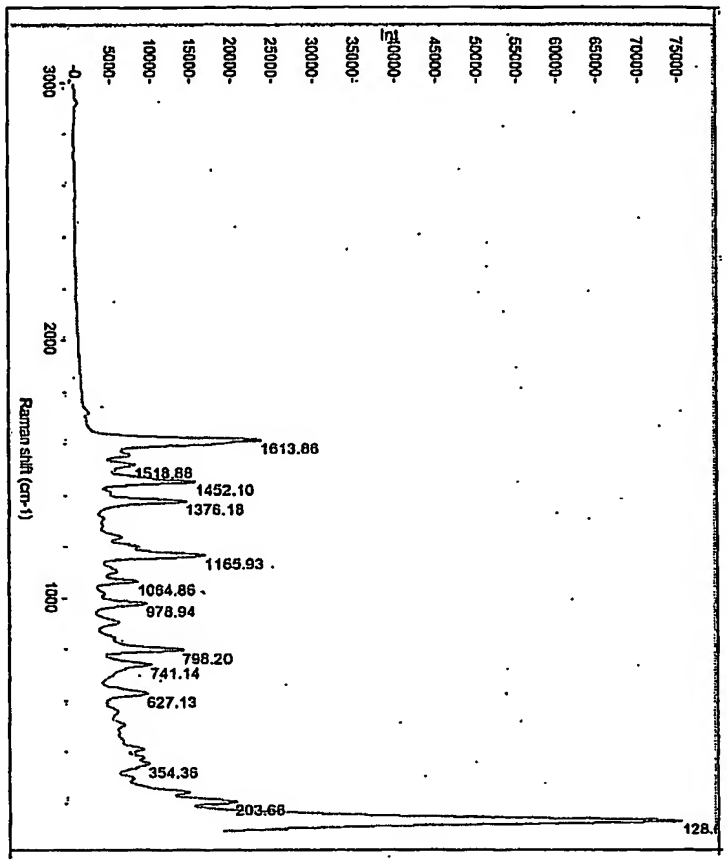

Int
0
5000
10000
15000
20000
25000
30000
35000
40000
45000
50000
55000
60000
65000
70000
75000
3000
2000
1000
Raman shift (cm-1)
1613.66
1518.68
1452.10
1376.18
1165.93
1084.86
978.94
798.20
741.14
627.13
354.36
203.66
128.

FIG. 33

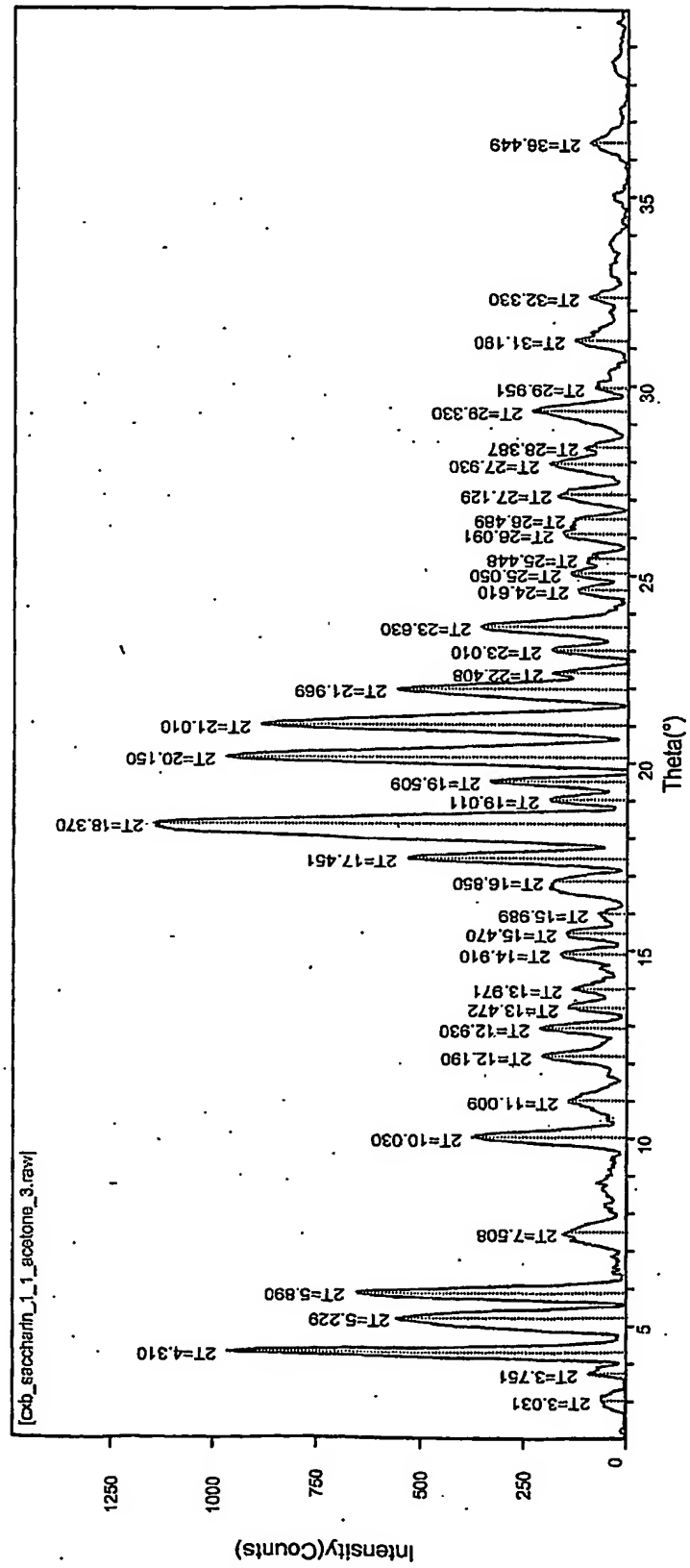

[Cxb_saccharin_1_1_acetone_3.raw]
2T=3.031
2T=3.751
2T=4.310
2T=5.229
2T=5.890
2T=7.508
2T=10.030
2T=11.009
2T=12.190
2T=12.930
2T=13.472
2T=13.871
2T=14.910
2T=15.470
2T=15.989
2T=16.850
2T=17.451
2T=18.370
2T=19.011
2T=19.509
2T=20.150
2T=21.010
2T=21.969
2T=22.408
2T=23.010
2T=23.630
2T=24.610
2T=25.050
2T=25.448
2T=26.091
2T=26.489
2T=27.129
2T=27.930
2T=28.387
2T=28.330
2T=29.951
2T=31.180
2T=32.330
2T=38.449
Intensity(Counts)
0
250
500
750
1000
1250
Theta(°)
5
10
15
20
25
30
35

FIG. 34

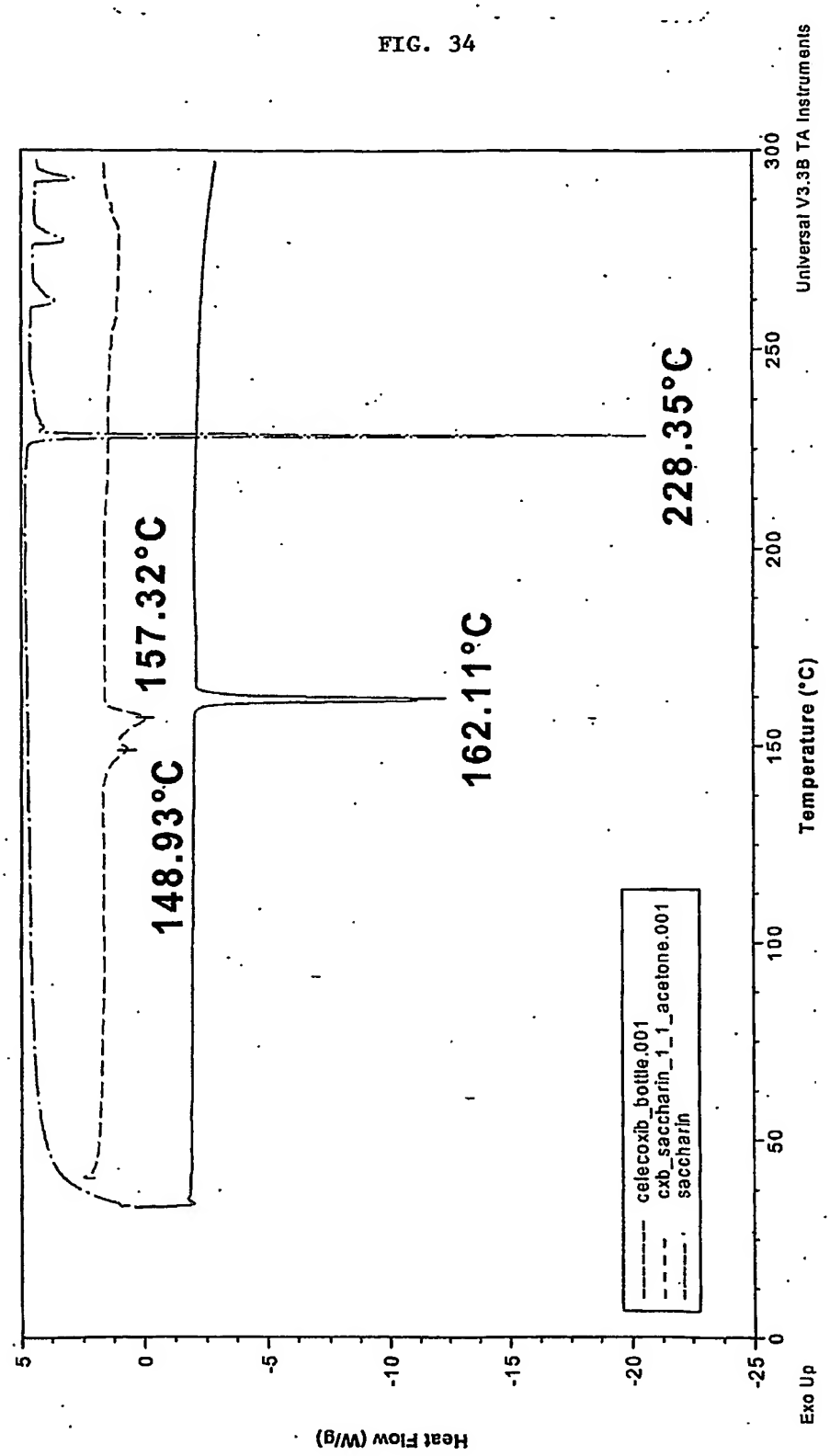

Universal V3.3B TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Up
148.93°C
157.32°C
162.11°C
228.35°C
celecoxib_bottle.001
cxb_saccharin_1_1_acetone.001
saccharin

FIG. 35

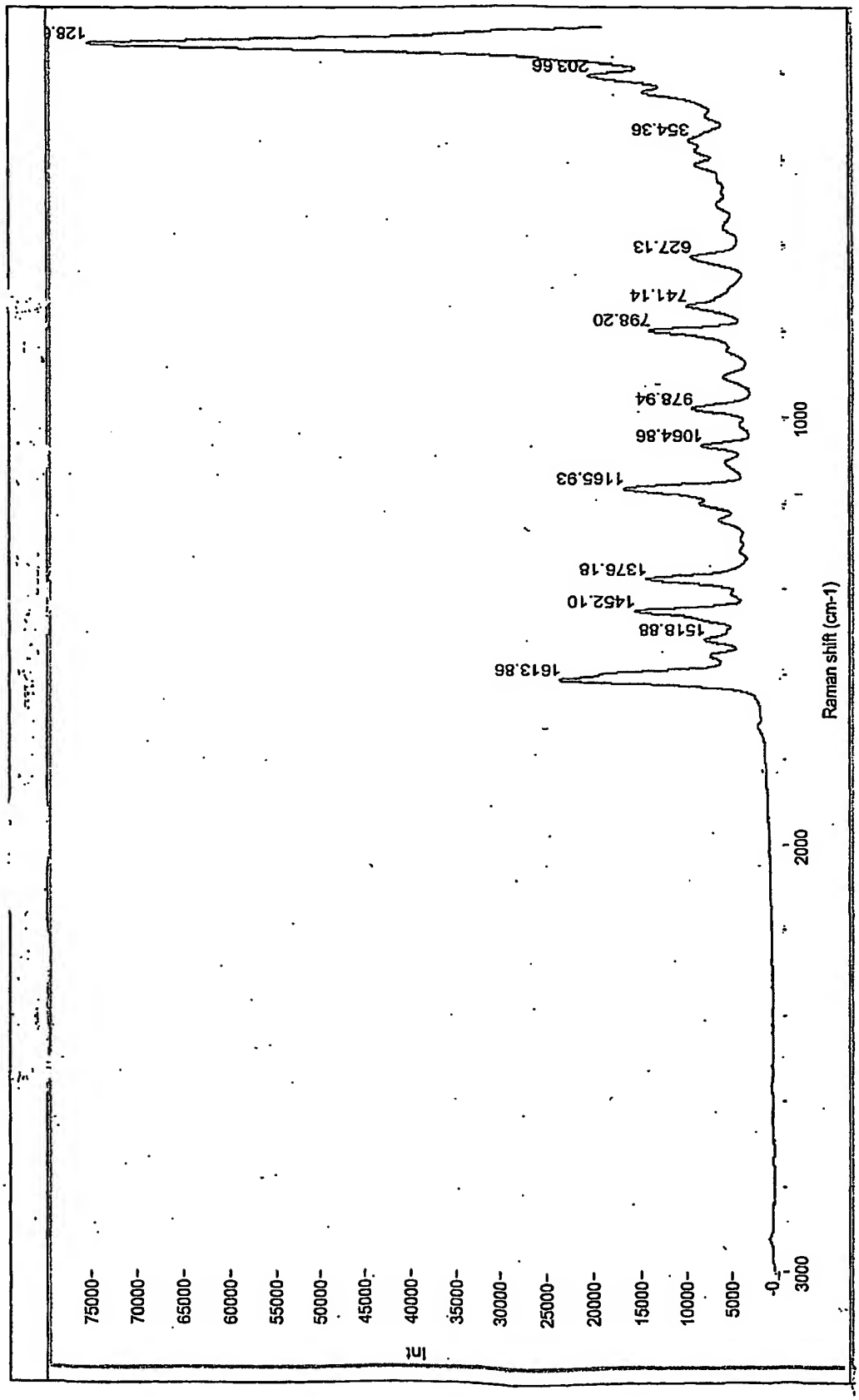

128.
203.66
354.36
627.13
741.14
798.20
978.94
1064.86
1165.93
1376.18
1452.10
1518.88
1613.86
Raman shift (cm-1)
1000
2000
3000
Int
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

FIG. 36

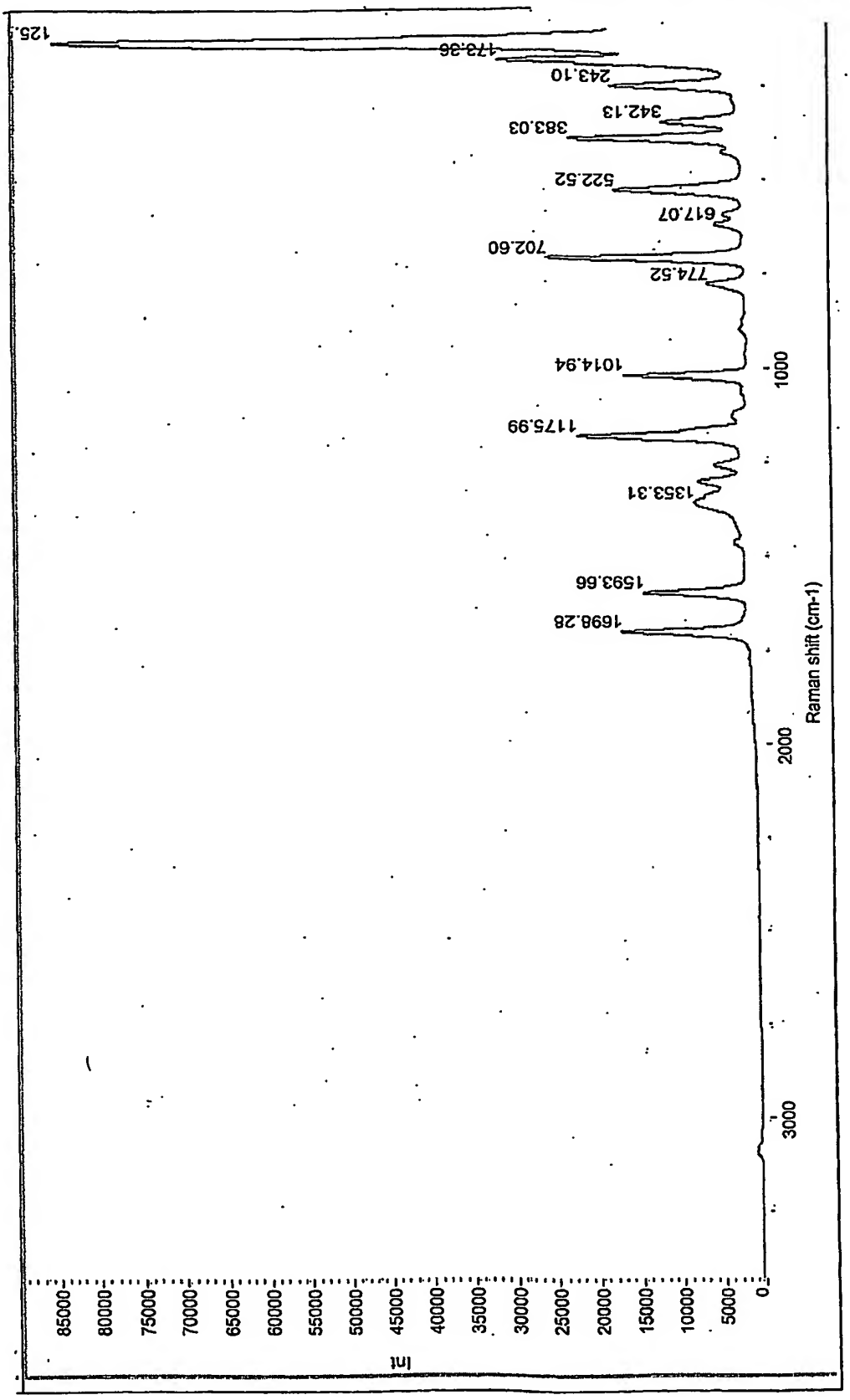
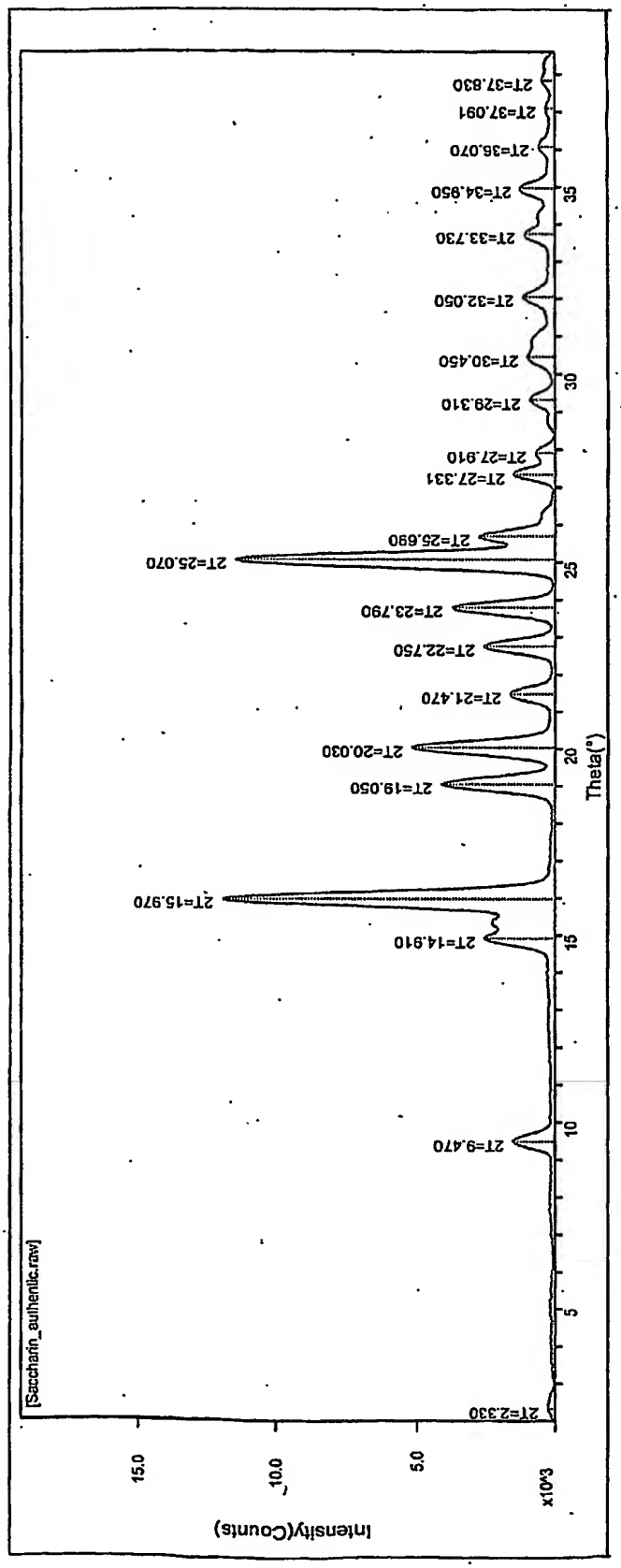

125.
173.36
243.10
342.13
383.03
522.52
617.07
702.60
774.52
1014.94
1175.99
1353.31
1593.66
1698.28
Raman shift (cm-1)
1000
2000
3000
Int
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

FIG. 37


Intensity(Counts)
15.0
10.0
5.0
x10^3
Theta(°)
5
10
15
20
25
30
35
[Saccharin_authentic.raw]
2T=2.330
2T=9.470
2T=14.910
2T=15.970
2T=19.050
2T=20.030
2T=21.470
2T=22.750
2T=23.790
2T=25.070
2T=25.690
2T=27.331
2T=27.910
2T=29.310
2T=30.450
2T=32.050
2T=33.730
2T=34.850
2T=36.070
2T=37.091
2T=37.830

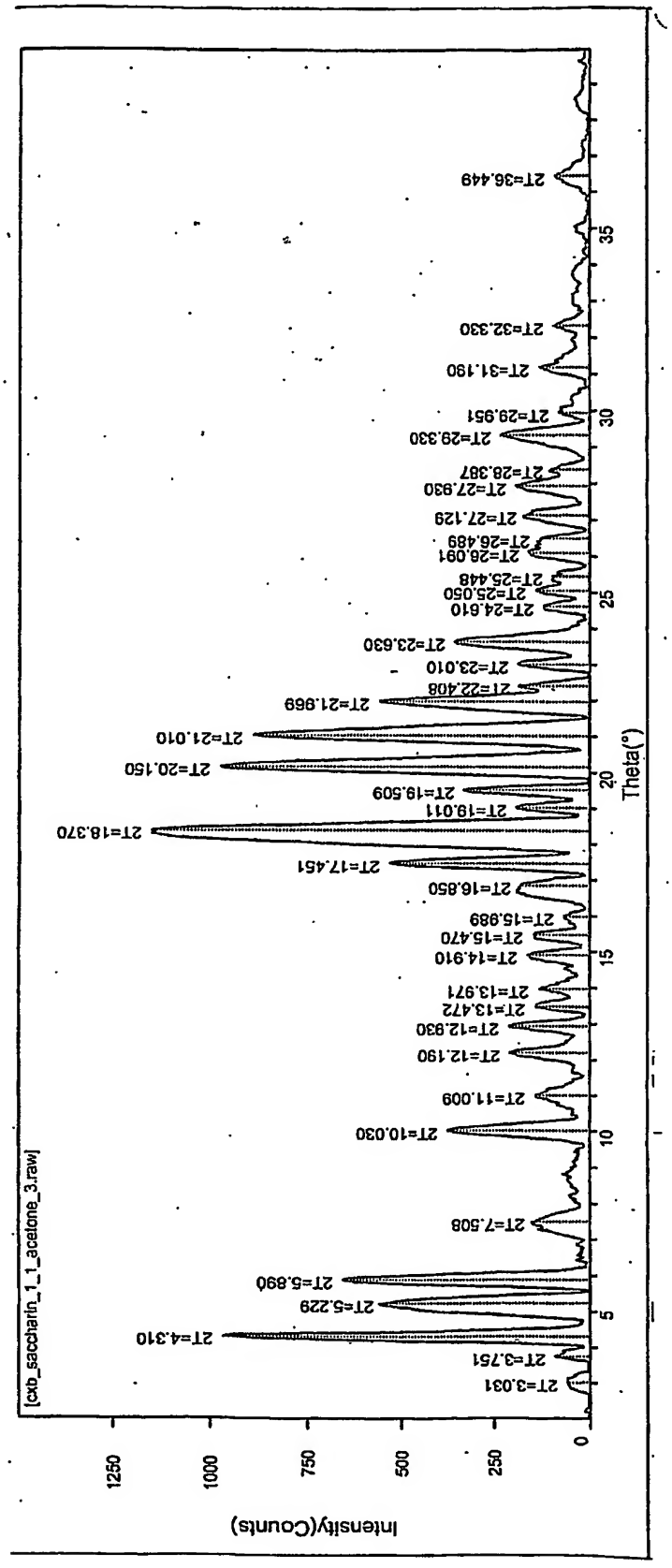

Intensity(Counts)
1250
1000
750
500
250
0
Theta(°)
5
10
15
20
25
30
35
[cxb_saccharin_1_1_acetone_3.raw]
2T=3.031
2T=3.751
2T=4.310
2T=5.229
2T=5.890
2T=7.508
2T=10.030
2T=11.009
2T=12.190
2T=12.830
2T=13.472
2T=13.971
2T=14.910
2T=15.470
2T=15.989
2T=16.850
2T=17.451
2T=18.370
2T=19.011
2T=19.509
2T=20.150
2T=21.010
2T=21.869
2T=22.408
2T=23.010
2T=23.630
2T=24.610
2T=25.050
2T=25.448
2T=26.091
2T=26.489
2T=27.129
2T=27.830
2T=28.387
2T=29.330
2T=29.951
2T=31.190
2T=32.330
2T=36.449

FIG. 38

FIG. 39

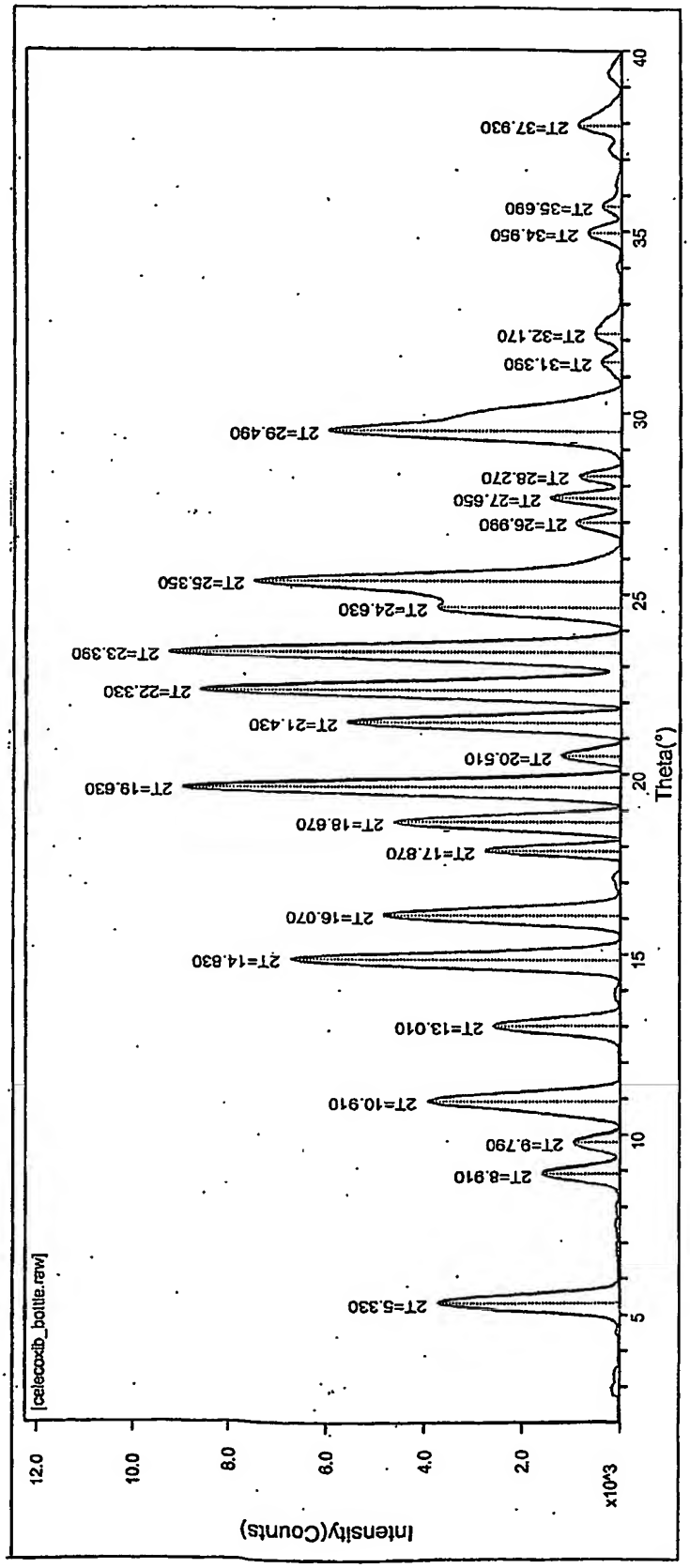

Intensity(Counts)
x10^3
12.0
10.0
8.0
6.0
4.0
2.0
Theta(°)
5
10
15
20
25
30
35
40
[celecoxib_bottle.raw]
2T=5.330
2T=8.910
2T=9.790
2T=10.910
2T=13.010
2T=14.830
2T=16.070
2T=17.870
2T=18.670
2T=19.630
2T=20.510
2T=21.430
2T=22.330
2T=23.390
2T=24.630
2T=25.350
2T=26.990
2T=27.650
2T=28.270
2T=29.490
2T=31.390
2T=32.170
2T=34.950
2T=35.690
2T=37.930

FIG. 40

Summary of powder diffraction data for starting materials and cocrystal		
Pure saccharin (2T = X°)	Pure celecoxib (2T = X°)	Celecoxib:Saccharin cocrystal (2T = X°)
9.470	5.330	4.310*
14.91	8.910	5.229
15.97	9.790	5.890*
19.05	10.91	7.508*
20.03	13.01	10.03*
21.47	14.83	11.01
22.75	16.07	12.19*
23.79	17.87	12.93
25.07	18.67	17.45
25.69	19.63	20.15

* Data represents peaks that are clearly unique to the cocrystal.

FIG. 41

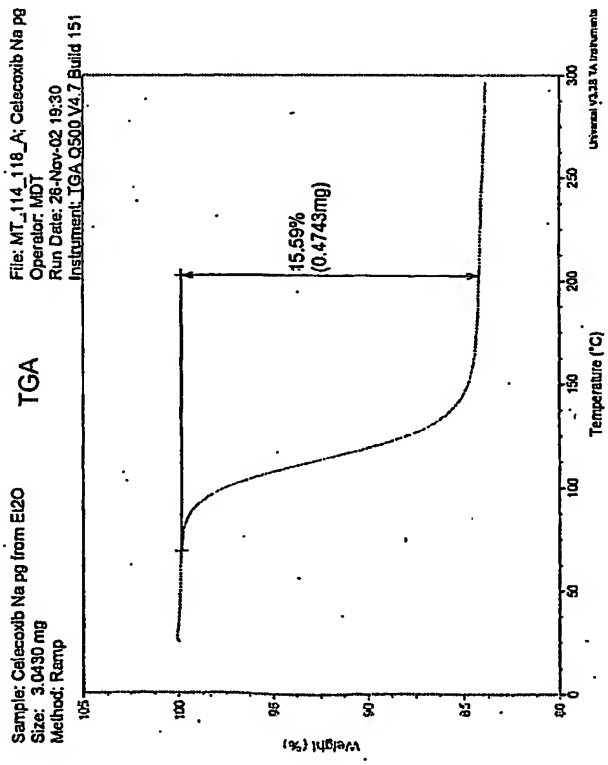

TGA
Sample: Celecoxib Na pg from Et2O
Size: 3.0430 mg
Method: Ramp
File: MT_114_118_A: Celecoxib Na pg
Operator: MDT
Run Date: 26-Nov-02 19:30
Instrument: TGA Q500 V4.7 Build 151
15.59%
(0.4743mg)
Weight (%)
Temperature (°C)
Universal V3.3B TA Instruments

FIG. 42

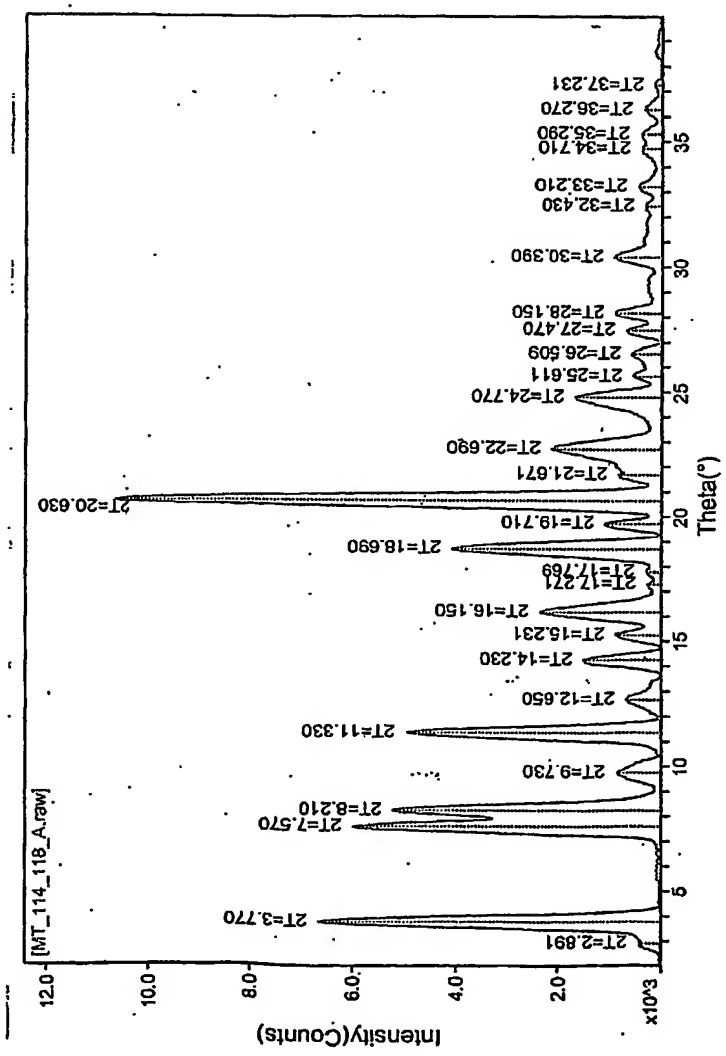

[MT_114_118_A.raw]
Intensity(Counts)
x10^3
12.0
10.0
8.0
6.0
4.0
2.0
Theta(°)
5
10
15
20
25
30
35
2T=2.891
2T=3.770
2T=7.570
2T=8.210
2T=9.730
2T=11.330
2T=12.650
2T=14.230
2T=15.231
2T=16.150
2T=17.221
2T=17.769
2T=18.690
2T=19.710
2T=20.630
2T=21.671
2T=22.690
2T=24.770
2T=25.611
2T=26.509
2T=27.470
2T=28.150
2T=30.390
2T=32.430
2T=33.210
2T=34.710
2T=35.290
2T=36.270
2T=37.231

FIG. 43

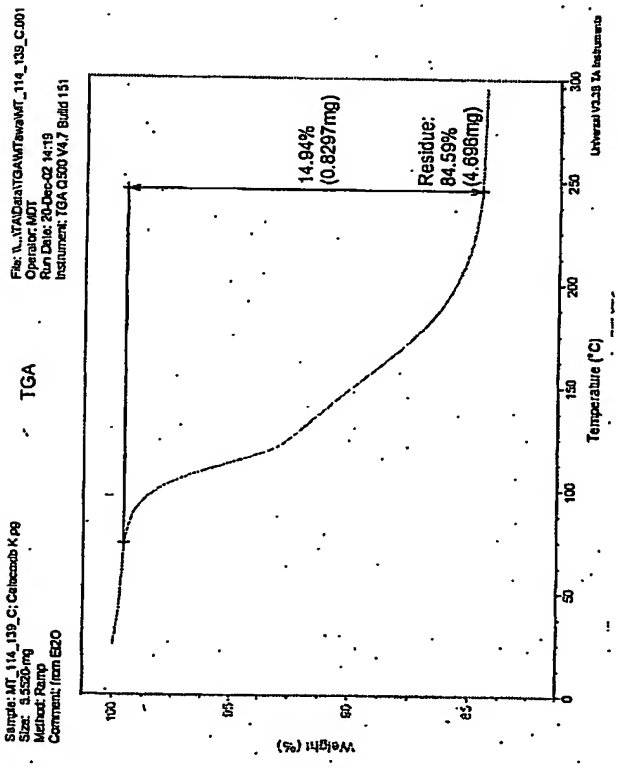
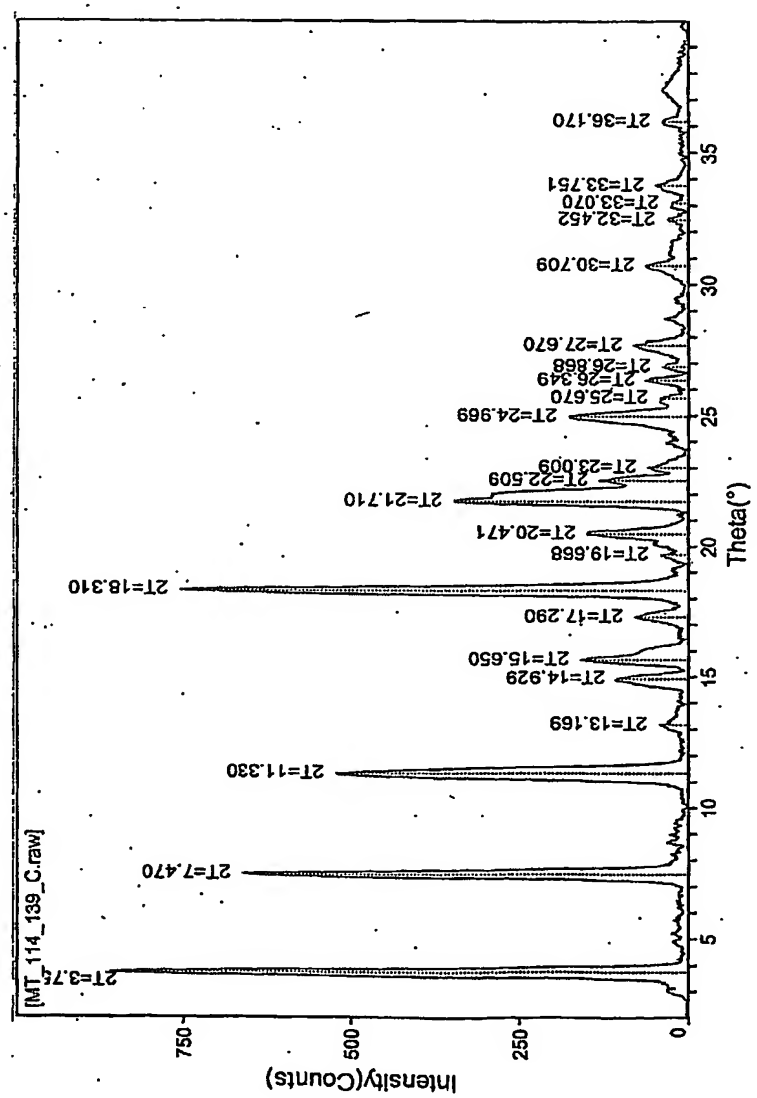

TGA
14.94%
(0.8297mg)
Residue:
84.59%
(4.698mg)
Weight (%)
Temperature (°C)
Universal V3.3B TA Instruments

FIG. 44


[MT_114_139_C.raw]
2T=3.744
2T=7.470
2T=11.330
2T=13.169
2T=14.929
2T=15.650
2T=17.290
2T=18.310
2T=19.668
2T=20.471
2T=21.710
2T=22.509
2T=23.009
2T=24.969
2T=25.670
2T=26.349
2T=26.868
2T=27.670
2T=30.709
2T=32.452
2T=33.070
2T=33.751
2T=36.170
Intensity(Counts)
0
250
500
750
Theta(°)
5
10
15
20
25
30
35

Docket No.: 3151.1004-003
Title: CRYSTALLINE SALTS OF CELECOXIB
Inventors: Örn Almarsson *et al.*

FIG. 45

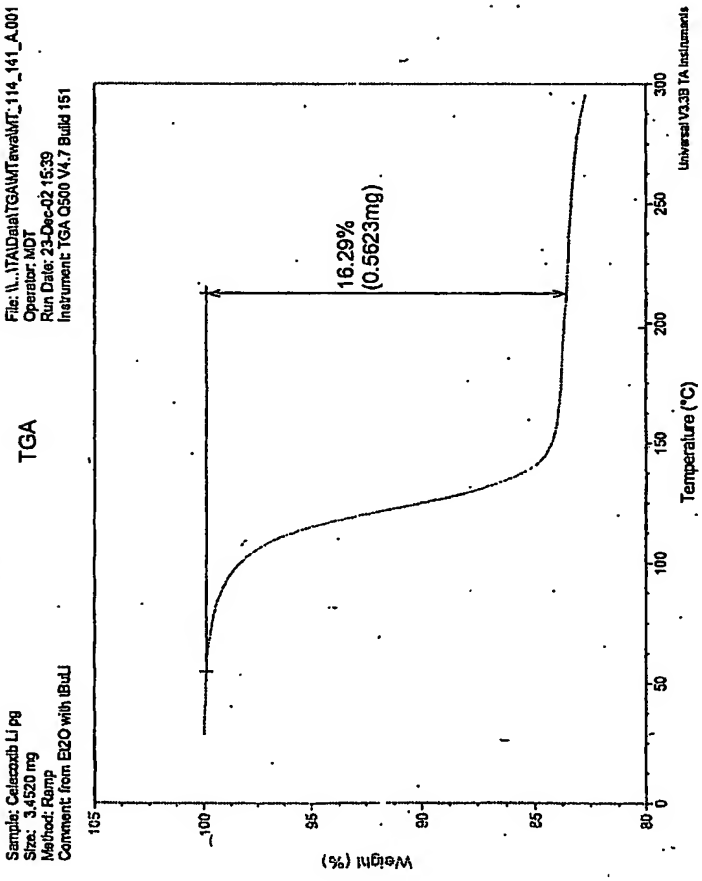
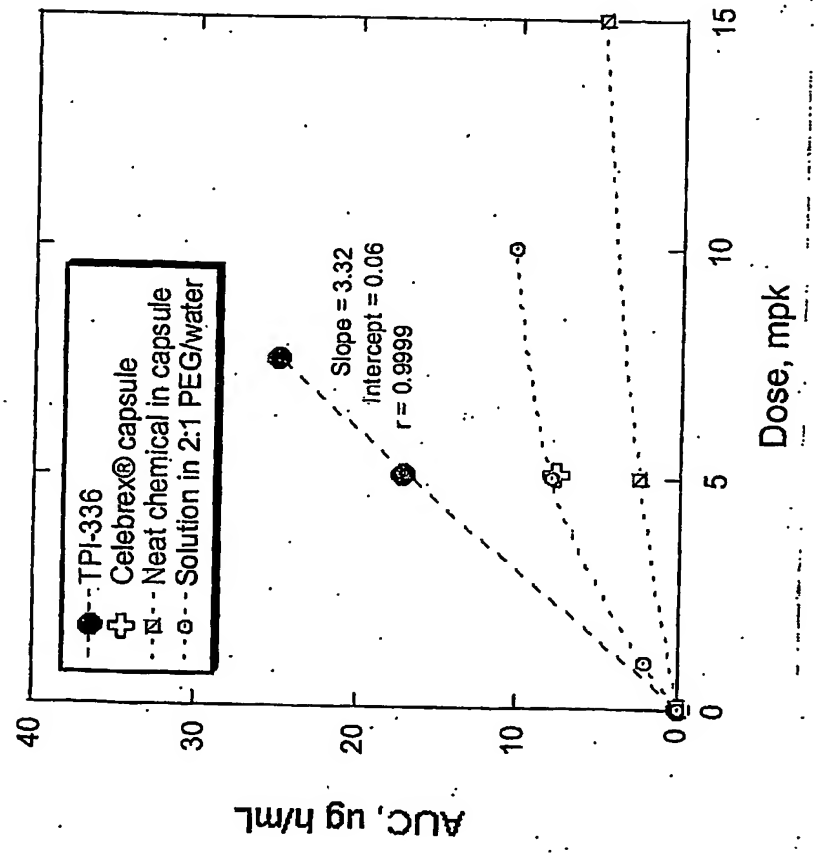


FIG. 46


AUC, ug h/mL
0
10
20
30
40
Dose, mpk
0
5
10
15
TPI-336
Celebrex® capsule
Neat chemical in capsule
Solution in 2:1 PEG/water
Slope = 3.32
Intercept = 0.06
r = 0.9999

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